Chapter 101

Spectral Analysis of R-R Variability to Evaluate Autonomic Physiology and Pharmacology and to Predict Cardiovascular Outcomes in Humans*

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OVERVIEW OF R-R VARIABILITY

R-R variability has been used for many years as a research tool, especially to evaluate the autonomic nervous system in short-term psychology experiments. Increasingly, R-R variability is being used to evaluate patients with cardiovascular diseases. It has been used to study cardiovascular physiology and pharmacology, and to predict risk of death or arrhythmic events in patients with coronary heart disease. Frequency domain measures of R-R variability are more commonly used for mechanistic studies because they resolve parasympathetic and sympathetic influences better than do time domain measures. A number of studies have indicated that spectral analysis of R-R variability provides a robust method for measuring vagal modulation of R-R intervals. Under special circumstances, spectral analysis of R-R variability can provide insight into the activity of the sympathetic nervous system as well. For prediction of death, time and frequency domain measures of R-R variability provide equivalent predictive information.

PHYSIOLOGICAL BASIS FOR THE USE OF SPECTRAL ANALYSIS OF R-R VARIABILITY FOR ARRHYTHMIA ASSESSMENT

Sympathetic Nervous System and Cardiac Arrhythmias

A large body of evidence indicates that the sympathetic nervous system promotes cardiac arrhythmias, especially malignant ventricular arrhythmias, such as ventricular tachycardia and ventricular fibrillation.[1-6] Increased sympathetic nervous activity is especially prone to contribute to cardiac arrhythmias when the heart is already scarred or becomes acutely ischemic. Increased sympathetic nervous activity increases the heterogeneity of refractoriness in different regions of the heart. This effect seems important in promoting arrhythmias.

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Parasympathetic Nervous System and Cardiac Arrhythmias

A Model of Sudden Cardiac Death. The parasympathetic nervous system plays a protective role, decreasing the likelihood of malignant ventricular arrhythmias. Some of the most impressive studies on vagal protection from malignant ventricular arrhythmias were performed in a dog model of sudden cardiac death developed by Schwartz, Stone, and colleagues.[6-9] A left thoracotomy was done and the anterior descending coronary artery was ligated to produce anterior myocardial infarction. During the same operation, a blood flow transducer and hydraulic occluder were placed around the circumflex coronary artery. Thirty or more days later, dogs were exercised 18 minutes on a treadmill to produce near maximal heart rates, about 200/min; after 17 minutes of exercise, the circumflex coronary artery was occluded for 2 minutes. The sudden coronary occlusion during exercise produced myocardial ischemia in the setting of decreased vagal and increased sympathetic activity. Under these circumstances, about half of the dogs developed ventricular fibrillation. The response to exercise/ischemia was quite reproducible; dogs that fibrillated repeatedly were classified as susceptible and dogs that did not were classified as not susceptible.

Baroreflex Sensitivity Predicts Ventricular Fibrillation. Billman et al.[10] showed that the response to the exercise/ischemia challenge could be predicted by baroreflex sensitivity. Baroreflex sensitivity was measured as the change in R-R interval in response to the increase in systolic blood pressure after intravenous injection of phenylephrine. On average, baroreflex sensitivity dropped after myocardial infarction; about 70% of dogs showed a substantial drop from preinfarction values. However, baroreflex sensitivity tended to maintain its rank order after infarction: that is, the dogs with the lowest preinfarction baroreflex sensitivity tended to have the lowest baroreflex sensitivity after infarction. Dogs with low baroreflex sensitivity were susceptible to ventricular fibrillation when challenged with the exercise/ischemia test, whereas dogs with high baroreflex sensitivity were not (Fig. 101–1). Susceptible dogs could be converted to non-susceptible status by exercise training, which increased baroreflex sensitivity,[11] suggesting that baroreflex sensitivity is not just an epiphenomenon associated with ischemic ventricular fibrillation but is part of the pathophysiological loop that causes ventricular fibrillation.

R-R Variability Predicts Ischemic Ventricular Fibrillation. A smaller set of experiments in the same model of sudden death

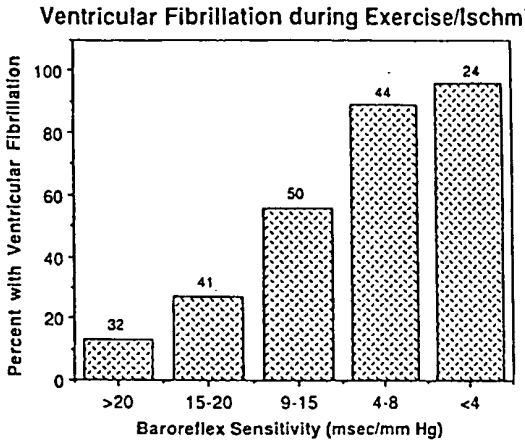

Figure 101–1. The probability of developing ventricular fibrillation during exercise and ischemia in dogs with previous myocardial infarction is inversely related to baroreflex sensitivity. The x-axis gives the categories for baroreflex sensitivity; the y-axis is the percentage of dogs that develop ventricular fibrillation during exercise and ischemia. The numbers over the bars indicate the number of dogs in each group. (Data from Schwartz PJ, et al: Circulation 78:969–979, 1988.)

showed that R-R variability drops substantially after experimental myocardial infarction in dogs.[12] Dogs with lower values for vagal measures of R-R variability after infarction have a much greater chance of developing ventricular fibrillation during the exercise/ischemia challenge.[12] However, preinfarction values for R-R variability did not predict postinfarction values or the response to the exercise/ischemia challenge, probably because the rank order for high-frequency R-R variability was not the same before and after infarction.[13]

METHODOLOGY

Frequency Domain Analysis

The goal of the frequency analysis of R-R interval data is to identify periodic components and to estimate their frequency and power. There is no single best way to accomplish this task. Choosing the most appropriate methods depends on the characteristics of the particular data under study (e.g., duration of recording, type of subjects, question being addressed) and the particular information required (e.g., entire spectrum or specific frequency bands).

Standard Frequency Bands. Power spectral measures of the R-R time series can delineate cyclic fluctuations in the R-R intervals in terms of their frequency and power. Table 101–1 lists the standard frequencies that are estimated for use in cardiac physiological or epidemiological studies. High-frequency (HF) power (0.15–0.40 Hz) estimates cyclical fluctuations with a nominal period of 2.5 to 6.7 seconds. To estimate HF power centered on 0.25 Hz, data should be collected for about 10 to 15 times the period of the fluctuations being estimated—that is, about 1 minute (4-second period × 15). For low-frequency (LF) power (0.04–0.15 Hz) centered on 0.10 Hz, data should be collected for about 2.5 minutes (10-second period × 15). Very LF power (0.0033–0.04 Hz) is usually estimated from 5 minutes of R-R interval data (0.0033 Hz is the lowest frequency in a 300-second period, i.e., 1/300 second); fluctuations with periods as long as 20 seconds can be estimated accurately from a 5-minute segment of R-R interval data. Figure 101–2 shows power spectra calculated for a 5-minute period. Below LF power (<0.04 Hz), R-R interval power spectra are log-linear and inversely related to the log of frequency—that is, the lower the frequency, the greater the power (so-called 1/f relationship).[14] Because of the 1/f relationship, power spectra measured on 24 hours of R-R interval data have more than 80% of their power in the frequency band below 0.0033 Hz (ultra-low-frequency power).

Response of R-R Power Spectra to Physiological Interventions. Physiological perturbations and pharmacological interventions help to define physiological systems responsible for cyclical fluctuations in the R-R intervals. HF power (0.15–0.40 Hz) repre-

Table 101–1. DEFINITIONS FOR TIME AND FREQUENCY DOMAIN MEASURES OF R-R VARIABILITY

Variable	Domain	Units	Definition
Night-day difference	Time	msec	Difference between the average of all the normal R-R intervals at night (24:00 to 05:00) and the average of all the normal R-R intervals during the day (07:30 to 21:30)
SDNN	Time	msec	Standard deviation of all normal R-R intervals in the entire 24-hour ECG recording
SDANN index	Time	msec	Standard deviation of the average normal R-R intervals for all 5-minute segments of a 24-hour ECG recording (each average is weighted by the fraction of the 5 minutes that has normal R-R intervals)
SDNN index	Time	msec	Mean of the standard deviations of all normal R-R intervals for all 5-minute segments of a 24-hour ECG recording
r-MSSD	Time	msec	Root mean square successive difference, the square root of the mean of the squared differences between adjacent normal R-R intervals during the entire 24-hour ECG recording
pNN50	Time	Percentage	Percentage of differences between adjacent normal R-R intervals that are greater than 50 msec computed during the entire 24-hour ECG recording
NN50	Time	None	Number of adjacent normal R-R intervals that are greater than 50 msec counted during the entire 24-hour ECG recording
Total power	Frequency	$msec^2$	Energy in the heart period power spectrum up to 0.40 Hz
Ultra low-frequency (ULF) power	Frequency	$msec^2$	Energy in the heart period power spectrum up to 0.0033 Hz
Very low-frequency (VLF) power	Frequency	$msec^2$	Energy in the heart period power spectrum between 0.0033 and 0.04 Hz
Low-frequency (LF) power	Frequency	$msec^2$	Energy in the heart period power spectrum between 0.04 and 0.15 Hz
High-frequency (HF) power	Frequency	$msec^2$	Energy in the heart period power spectrum between 0.15 and 0.40 Hz
LF/HF ratio	Frequency	None	Ratio of LF to HF power

From Bigger JT Jr, et al: Am J Cardiol 69:891–898, 1992.

sents a pure vagal efferent signal that is modulated by ventilation (respiratory sinus arrhythmia).[15-19] The HF peak varies with ventilatory frequency and usually is found at a frequency of about 0.25 Hz, corresponding to 15 breaths per minute. Several studies have used breathing cued to a metronome to show that the peak of HF power moves to the frequency of breathing.[20, 21] HF power disappears almost totally after intravenous injection of atropine, indicating that the efferent neural signal travels on the vagus nerve.[20, 21] LF power (0.04–0.15 Hz) has contributions from vagal and sympathetic modulation of R-R intervals.[18-21] LF power seems to modulate on the spontaneous cycling of arterial blood pressure (i.e., the Mayer waves) at a frequency of about 0.10 Hz. The ratio of LF to HF power is a useful index of sympathetic/parasympathetic balance, especially during postural changes. On standing, HF power decreases to about 25% of its supine value; LF power decreases slightly or increases (Fig. 101–2). Thus, the LF/HF ratio increases substantially. The increase is attributed to an increase in Mayer waves on standing or being tilted upright and/or the increased baroreflex sensitivity in the upright posture.[20] The LF power in the supine position is abolished by atropine; the increase in LF/HF ratio seen on standing or being tilted upright is attenuated markedly after β-adrenergic blockade.[20, 21] For physiological or pharmacological studies (e.g., effect of posture, breathing maneuvers, drug effects), power spectra obtained from a series of R-R intervals (heart period or R-R variability) or from a series of instantaneous heart rates (heart rate variability) yield virtually identical results. However, in correlations and multivariate analyses, heart period (R-R) variability and heart rate variability are not equivalent. For example, the standard deviation of instantaneous heart rate has almost no correlation with average heart rate, whereas the standard deviation of normal R-R intervals has a modest correlation with average R-R interval ($r = 0.50$).

Although somewhat crude, HF and LF power in a power spectrum of the R-R time series can provide important information about the autonomic nervous system in intact humans during normal daily activities. Spectral analysis can provide information on the autonomic nervous system non-invasively and inexpensively, which makes the test feasible to use in large-scale epidemiological studies or clinical trials. Also, the methodology lends itself to physiological and pharmacological studies that measure autonomic nervous activity before and after an intervention.

Correlations Among Frequency and Time Domain Measures of R-R Variability. Table 101–1 lists time and frequency domain measures that have been used to assess R-R variability in cardiovascular diseases. In 715 patients with myocardial infarction, Bigger et al.[22] determined the correlations among time and frequency domain measures of R-R variability and the predictive value of time domain measures of R-R variability for death during follow-up after acute myocardial infarction. Table 101–2 shows that each of the frequency domain measures of R-R variability had one or two corresponding variables in the time domain that correlated with it so strongly ($r \geq 0.90$) that the variables were essentially equivalent:

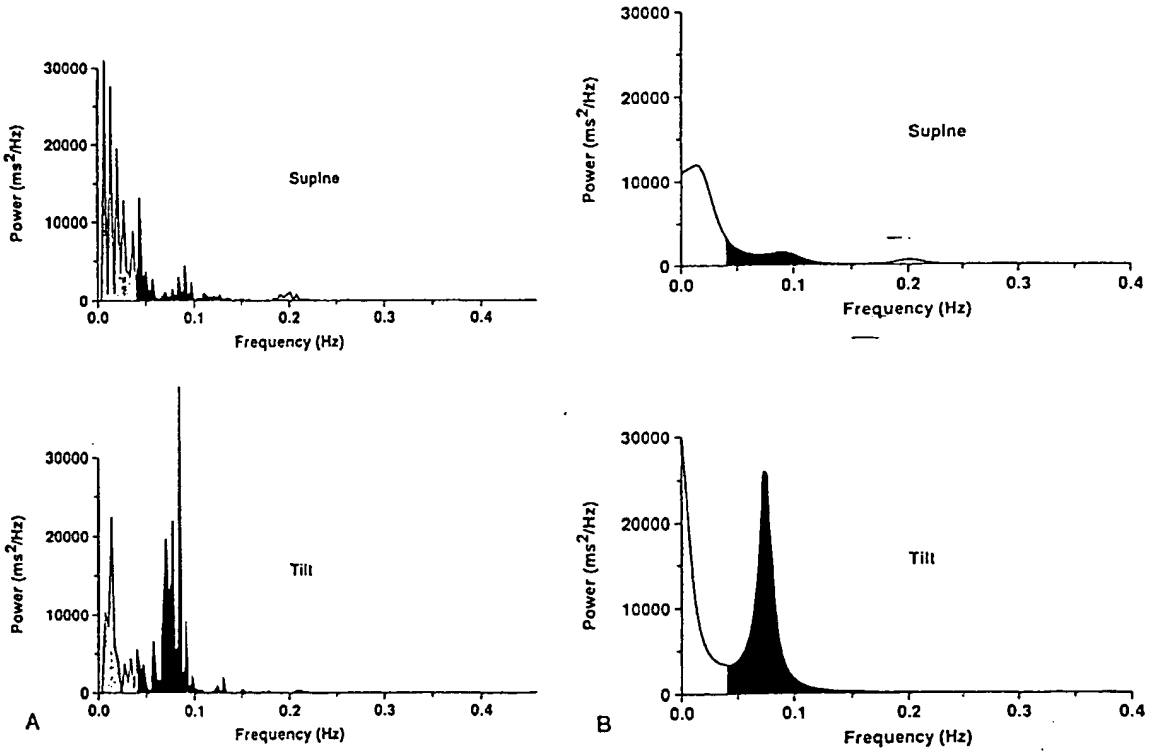

Figure 101–2. Power spectral analysis of R-R interval time series. *A*, FFT analysis of two 5-minute recordings of R-R intervals. The upper panel shows the FFT of a recording made supine and resting; the lower panel shows the FFT of a recording made during 60-degree head-up tilt. *B*, Results of autoregression analysis of the same two 5-minute recordings. The mathematical algorithm smooths the data, but gives almost identical areas under the curves in the frequency bands of interest. In the supine recording, there is a peak at about 0.20 Hz in the HF power band, and a peak at about 0.08 Hz in the LF power band. More than half the power is in the VLF power band. Both methods show a decrease in HF power and a marked increase in LF power during head-up tilt.

Table 101–2. CORRELATIONS AMONG MEASURES OF R-R VARIABILITY (N = 715)

Variable	Night-Day Difference	SDNN	Ln Total Power	LN ULF Power	SDANN Index	Ln VLF Power	SDNN Index	Ln LF Power	Ln r-MSSD	Ln pNN50	Ln HF Power	Ln LF/HF Power
Night-day difference	1.00											
SDNN	0.71	1.00										
Ln total power	0.68	0.96	1.00									
Ln ULF power	0.71	0.95	0.99	1.00								
SDANN index	0.75	0.98	0.94	0.96	1.00							
Ln VLF power	0.43	0.78	0.82	0.75	0.68	1.00						
SDNN index	0.44	0.82	0.79	0.71	0.70	0.90	1.00					
Ln LF power	0.42	0.72	0.75	0.67	0.61	0.91	0.89	1.00				
Ln r-MSSD	0.28	0.62	0.58	0.52	0.51	0.60	0.78	0.65	1.00			
Ln pNN50	0.27	0.57	0.56	0.50	0.49	0.59	0.71	0.64	0.93	1.00		
Ln HF power	0.35	0.67	0.66	0.59	0.57	0.70	0.82	0.77	0.92	0.89	1.00	
Ln LF/HF power	0.17	0.20	0.26	0.23	0.17	0.45	0.25	0.49	−0.25	−0.22	−0.18	1.00

Ln, natural logarithm; LF, low frequency; HF, high frequency; ULF, ultra low frequency; VLF, very low frequency.
From Bigger JT Jr, et al: Am J Cardiol 69:891–898, 1992.

ultra-low-frequency power with standard deviation of the normal (SDNN) and abnormal (SDANN) R-R interval indices, very-low-frequency power, and LF power with SDNN index, and HF power with r-MSSD and pNN50. As expected from theoretical considerations, SDNN and the square root of total power were almost perfectly correlated ($r \approx 1.0$). Strongly correlated time and frequency domain measures of R-R variability have equivalent ability to predict death.

Technical Issues for Power Spectral Analysis

QRS Labels. The requirement for accurate QRS labeling is more demanding for power spectral analysis than for the usual Holter analysis. When a Holter is analyzed for ectopic activity, substantial effort is expended to correctly label ventricular premature complexes, but atrial premature complexes are often considered of less importance. For power spectral analysis of R-R variability, it is equally important to recognize atrial premature complexes and noise that has been incorrectly labeled as QRS complexes by the computer. It is especially important to label QRS complexes accurately when R-R variability is small, because most of the energy in the power spectrum may be produced by a few misclassified QRS complexes.

Dealing with Missing Data and Ectopic Complexes. In patients with heart disease, the sequence of R-R intervals often contains many ectopic complexes, but measurements of R-R variability generally are concerned only with normal R-R (N-N) intervals. In time domain analysis, non-N-N intervals and sometimes adjacent intervals can just be excluded. However, for frequency analysis, it is important to maintain the temporal ordering and spacing of the sequence of N-N intervals. Albrecht and Cohen[23] evaluated methods for dealing with missing QRSs in a sequence of R-R intervals to avoid errors in the estimation of the R-R power spectrum. Simple linear splining gave better results than more complicated, theoretically better, methods. Linear splining reduces HF components of the power spectrum by a small amount, without substantially perturbing LF components. After splining, the resulting data are suitable for efficient computational methods based on the fast Fourier transform.

Sampling the R-R Interval Sequence. Berger et al.[24] showed that sampling of the instantaneous R-R intervals at fixed time intervals (e.g., 250–330 msec) generates an unbiased time series. A "boxcar" filter with a window wider than that of the sampling interval minimizes artifacts from the sampling process. This method of sampling and filtering can attenuate HF power (about 5%–8% at 0.40 Hz) but also can be corrected accurately.[24, 25]

Methods of Spectral Analysis

Spectral estimation is a large topic and an area of active research in mathematics, statistics, and signal processing. There is no "best" method of spectral estimation, but two methods are widely used—the Fourier transform and autoregression.[26]

The Fourier Transform. In "classical spectral analysis," the Fourier transform represents the R-R time series as a sum of periodical functions.[27] These techniques for estimating periodical components have been used with experimental data since the 19th century, and a rich statistical literature is available. Efficient mathematical algorithms for computing the Fourier transform were reported by Cooley and Tukey.[28] The total power of the periodogram equals the variance of the original R-R sequence. The Fourier transform decomposes the variance of the input data into the variance attributable to each specific frequency (see Fig. 101–2*A*).[29] The existence of efficient and standard computational techniques, the simple theoretical basis for the transform, and the existence of a complete statistical theory for analyzing the distribution characteristics of the resulting estimates have made the discrete Fourier transform the most commonly used method for frequency domain analysis of R-R interval data.

Autoregression (Parametric Identification Techniques). Yule performed spectral analysis with an alternative method in which a linear predictive model is fitted to time series data.[30] As applied to the analysis of R-R variability, regression techniques are used to predict the present R-R interval from a linear combination of the immediately preceding R-R intervals. The popularity of these parametric identification techniques has increased with the development of efficient computational algorithms.[31] Compared with classical spectral analysis, autoregression techniques permit a signal to be represented as a sum of a smaller number of periodical components chosen at specific frequencies. For analysis of R-R variability data, the ability to obtain a small number of discrete frequencies has been the primary motivation for these techniques.[32] Because autoregression techniques construct the spectrum from a mathematical function, the spectrum is smooth and the HF peak resulting from respiratory (vagal) modulation of R-R intervals is clearly visible (see Fig. 101–2*B*).

Other Techniques. Other techniques are being explored for spectral analysis of R-R interval data. These include complex demodulation,[27, 33, 34] hypothesis-driven signal processing,[21] and nonlinear dynamics.[35, 36] These techniques have been discussed elsewhere.[37] Because these techniques are new and not yet standardized, it is important that studies using these techniques describe their computational procedures completely.

SPECTRAL ANALYSIS OF R-R VARIABILITY TO PREDICT DEATH AND ARRHYTHMIC EVENTS AFTER MYOCARDIAL INFARCTION

The precise role of spectral analysis of R-R variability in arrhythmia assessment is still being evaluated. However, it is already clear that in patients with coronary heart disease, power spectral measures of R-R variability can identify patients who have a high risk of developing malignant ventricular arrhythmias and death. Spectral analysis alone is a strong predictor of malignant ventricular arrhythmias or death. Spectral analysis of R-R variability predicts these outcomes independently of other risk predictors, such as ventricular arrhythmias or left ventricular dysfunction. As a result, spectral analysis substantially improves predictive accuracy when added to other risk predictors.

Prediction of Hospital Mortality After Myocardial Infarction by R-R Variability

R-R Variance Measured on Admission to the Coronary Care Unit. A substantial body of evidence has accumulated to indicate that measures of R-R variability in the time or frequency domains are excellent predictors of mortality after myocardial infarction. The first report of an association between R-R variability and prognosis was published by Wolf et al. in 1978.[38] These researchers studied 176 patients admitted to the hospital for acute myocardial infarction. A 60-second electrocardiographic (ECG) recording was made on the day of admission to the coronary care unit, and short-term R-R variability was estimated as the variance of 30 consecutive R-R intervals. Variance over such a short time interval primarily measures respiratory sinus arrhythmia (i.e., vagal activity modulated by breathing). Wolf et al. arbitrarily dichotomized their group using a variance of 1000 msec^2; 73 patients (42%) had sinus arrhythmia (variance $\geq$ 1000 msec^2) and 103 patients (59%) did not (Table 101–3). The mean age in the two groups was almost the same (56 and 57 years), but patients with R-R variances below 1000 msec^2 were more likely to have anterior myocardial infarction, Norris indices of 10 or above, low values for average R-R interval, and admission to a hospital a longer time after onset of chest pain.

The study by Wolf et al. showed that R-R variance measured over a period of less than 30 seconds predicted mortality during the next 9 to 14 days.[38] The hospital mortality of patients with R-R variances below 1000 msec^2 was 15.5% compared with 4.1% for patients with R-R variances of 1000 msec^2 or higher, a relative risk of 3.8. After adjusting for heart rate and location of the infarct, low R-R variance was still significantly associated with higher mortality rates. Only 19 deaths occurred in the group studied by Wolf et al., so that the strength of the association was not estimated precisely (95% confidence interval for the relative risk, 1.1–12.5). Also, no account was taken of left ventricular function, ventricular arrhythmias, or myocardial ischemia as covariates, so the independent predictive value of R-R variability was not evaluated. Nevertheless, this study was the first to call attention to the possible prognostic significance for short-term (vagal) measures of R-R variability made early after myocardial infarction.

Prediction of Long-Term Mortality by the Standard Deviation of Normal R-R Intervals

In 1987, Kleiger et al.[39] reported the predictive value of another time domain measure, the SDNN, calculated during a 24-hour period predicted death. This measure of R-R variability correlated very strongly with total power in a 24-hour R-R power spectrum and primarily measures ultra-slow oscillations in R-R intervals.[22]

Table 101–3. R-R VARIANCE AND HOSPITAL MORTALITY

Variance (msec^2)	Hospital Death		Total
	Yes	*No*	
<1000	16 (15.5%)	87	103
≥100	3 (4.1%)	70	73
Total	19	157	176

Relative risk = 3.8.
From Wolf M, Varigos G, Hunt D, Sloman J: Sinus arrhythmia in acute myocardial infarction. Med J Aust 2:52–53, 1978. Copyright 1978, The Medical Journal of Australia. Reproduced with permission.

This study included 808 patients and 127 deaths. The 24-hour Holter recordings were made 11 ± 3 days after acute myocardial infarction, at the time of discharge from the hospital. These investigators arbitrarily chose a SDNN value of 50 msec to divide their group into 125 patients (16%) with low values and 683 patients (84%) with high values. During 2 to 4 years of follow-up, the mortality rate of patients with SDNN values below 50 msec was 34% compared with a 12% mortality rate in patients with SDNN values of 50 msec or more, a relative risk of 2.8 (Fig. 101–3). Because of the large number of deaths, this relative risk is estimated precisely (95% confidence interval, 2.0–3.8). The SDNN predicted mortality independent of previously known risk predictors such as left ventricular ejection fraction or ventricular arrhythmia. This study was the first to show the independent predictive value of long-term measures of R-R variability for all-cause mortality after myocardial infarction.

Power Spectral Analysis to Predict Death After Acute Myocardial Infarction

Bigger et al.[40] studied 715 patients 2 weeks after myocardial infarction to establish the associations between six frequency domain (power spectral) measures of R-R period variability and mortality during 4 years of follow-up before and after adjusting for five previously established risk predictors.

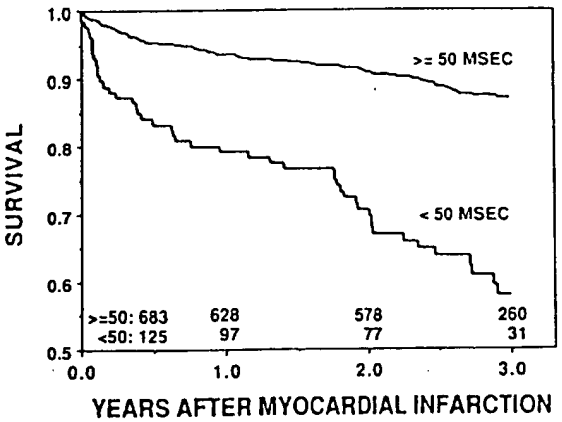

Figure 101–3. Survival as a function of the 24-hour standard deviation of normal R-R (N-N) intervals (SDNN) in 808 patients with myocardial infarction. Time after myocardial infarction is plotted on the x-axis; proportion surviving is plotted on the y-axis. (Data from Kleiger RE, et al: Am J Cardiol 59:256–262, 1987.)

Power Spectral Measures of R-R Variability. Six measures were calculated from spectral analysis of continuous 24-hour ECG recordings using fast Fourier transforms.[40] Power was calculated for four frequency bands of the 24-hour periodogram: (1) below 0.0033 Hz, ultra-low-frequency (ULF) power; (2) 0.0033 to below 0.04 Hz, very-low-frequency (VLF) power, which shows a relative increase in patients with congestive heart failure[41] and is the lowest frequency band that can be estimated in a 5-minute interval[24]; (3) 0.04 to below 0.15 Hz, LF power, which reflects modulation of sympathetic or parasympathetic tone by baroreflex activity;[15] and (4) 0.15 to 0.40 Hz, HF power, which reflects vagal modulation of R-R intervals, motivated primarily by ventilation.[16, 17] In addition, they calculated total power (power in the band of 0.40 Hz or less) and the ratio of LF to HF power, a measure that has been used as an indicator of sympathovagal balance.[21] High values for the ratio suggest predominance of sympathetic nervous activity relative to vagal activity. The 24-hour recordings were digitized without benefit of phase lock loop; therefore, flutter and wow artifact could cause small (<4%) increases in the HF power band (0.15–0.40 Hz). Figure 101–4 compares total power and its fractional distribution in patients with myocardial infarction with age- and sex-matched normal subjects. Total power is reduced markedly by myocardial infarction, but its fractional distribution does not change substantially. For normal subjects and patients with recent myocardial infarction, more than 80% of total power in a 24-hour power spectrum is in the ULF component and only about 2% in the HF component.[22]

Univariate Association of R-R Variability and Death. Bigger et al.[40] evaluated the association between the six frequency domain measures of R-R variability and three mortality end points: death from all causes, cardiac death, and arrhythmic death by the Hinkle-Thaler definition.[42] Results using all-cause mortality as the end point are shown in Figure 101–5. Each frequency domain measure of R-R variability had a significant and at least moderately strong univariate association with all-cause mortality, cardiac death, and arrhythmic death. Power in the lower frequency bands—ULF and VLF power—had stronger associations with all three mortality end points than power in the higher frequency bands—LF and HF power. The 24-hour total power also had a significant and strong association with all three mortality end points. For most frequency bands, the strength of association with the three mortality end points was similar. VLF power was the only variable that was more strongly associated with arrhythmic death than with cardiac death or all-cause mortality.[40] Until this finding is validated in another large study, it will not be clear whether it is a true or just a chance finding. Time domain measures of R-R variability, especially those that measure ULF, VLF, and LF power, also were strongly and independently associated with death during follow-up.[22]

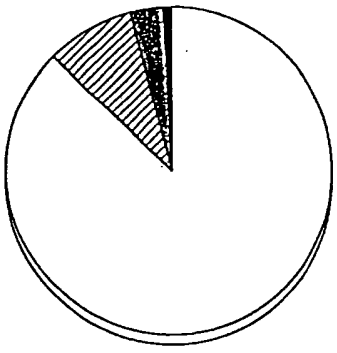

Figure 101–4. The effect of myocardial infarction on R-R variability. Data from 215 normal middle-aged men and women are shown above, and data from a group of patients with recent myocardial infarction are shown below. The area in the circles is proportional to total power calculated from a 24-hour R-R interval time series. Myocardial infarction causes a marked reduction in total power, but there is no significant change in the fractional distribution of power among the four frequency bands of interest. (Data from Bigger JT, et al: Am J Cardiol 69:891–898, 1992.)

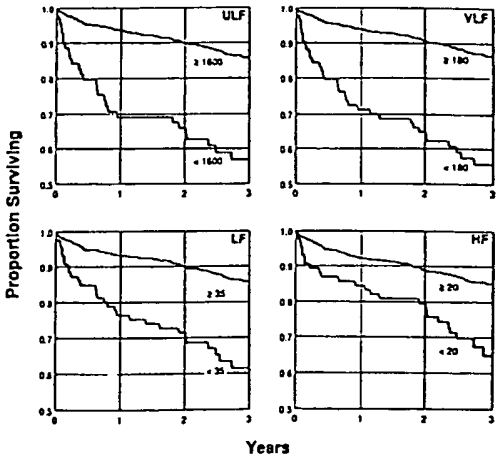

Figure 101–5. Kaplan-Meier survival curves for 715 patients in the high or low category for the four mutually exclusive frequency domain measures of heart period variability, ULF, VLF, LF, and HF power, using all-cause mortality as the end point. (Reproduced with permission from Bigger JT Jr, Fleiss JL, Steinman RC, et al: Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 85:164–171, 1992. Copyright 1992, American Heart Association.)

Multivariate Analyses with Power Spectral Measures of R-R Variability. To evaluate the independent associations between frequency domain measures of R-R variability and death of all causes, multivariate Cox regression models were used.[43, 44] A step-up procedure was used to add variables to the Cox model in order of their predictive value. Using this procedure, ULF power was selected first—that is, had the strongest association with death of all causes. Adding VLF power or LF power to ULF power in the Cox regression model significantly improved the prediction of outcome. With both ULF power and VLF power in the Cox regression model, the addition of LF and HF power, singly or together, did not significantly improve the prediction of all-cause mortality.[40] To determine how much predictive value frequency domain measures of R-R variability add to previously established postinfarction risk predictors, the strength of the relationship between the R-R variability measures and all-cause mortality, cardiac death, and arrhythmic death was evaluated before and after adjusting for five previously established postinfarction risk predictors: age, New York Heart Association (NYHA) functional class, rales in the coronary care unit,

left ventricular ejection fraction, and ventricular arrhythmias quantified in a 24-hour Holter ECG recording.[40] After adjustment for the five risk predictors, the association between mortality and total power, ULF power, and VLF power remained significant and strong, whereas LF power and HF power had only moderately strong association with mortality. The tendency for VLF power to be more strongly associated with arrhythmic death than with all-cause or cardiac death was still evident after adjusting for the five covariates.

Improved Prediction of Death Using R-R Variability Combined with Other Risk Predictors. Correlations between time or frequency domain measures of R-R variability and previously identified postinfarction risk predictors (e.g., left ventricular ejection fraction and ventricular arrhythmias) are remarkably weak.[22] The strongest correlation is with R-R interval itself (r = 0.52). However, Fleiss et al.[45] showed that adjusting for heart rate in various ways, e.g., coefficient of variation, did not improve the prediction of mortality compared with using R-R variability without any adjustment for heart rate. The lack of correlation between R-R variability and previously established postinfarction risk predictors suggests that measures of R-R variability will improve the identification of patients at high risk after myocardial infarction. Adding power spectral measures of R-R variability, made about 10 days after myocardial infarction, to previously known postinfarction risk predictors identified small subgroups with a 2.5-year mortality risk of approximately 50% (Fig. 101–6).[40] Predictive accuracy in the 50% range has never before been achieved in groups of patients studied after myocardial infarction. These results should be considered preliminary since the high risk groups are small and the 95% confidence intervals around the point estimates of the predictive accuracies are wide. If validated in larger studies or in meta-analyses, such high values for predictive accuracy have important implications for postinfarction assessment and management strategies.[46]

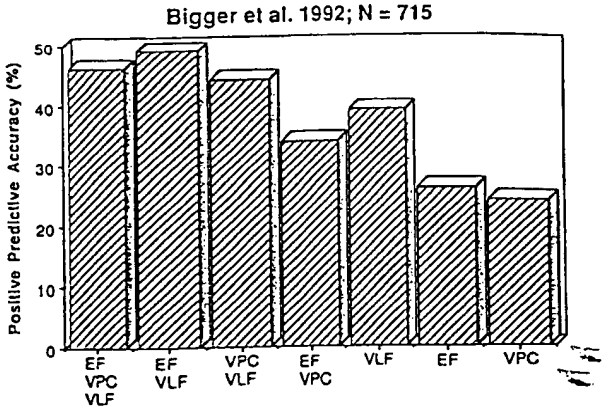

Figure 101–6. Improving positive predictive accuracy using combinations of risk predictors after myocardial infarction. Left ventricular ejection fraction (EF) or ventricular premature complexes (VPC) have a modest positive predictive accuracy for arrhythmic events when used alone (about 25%) or together (about 35%). Very low frequency power (VLF) alone has a better positive predictive accuracy (almost 40%). The positive predictive accuracy increases to 45% to 50% when VLF power is combined with either EF or VPC or both. (Data from Bigger JT Jr, et al: Circulation 85:164–171, 1992.)

Short-term Measures of R-R Variability to Predict Death After Myocardial Infarction

Bigger et al.[47] studied 715 patients 2 weeks after myocardial infarction to test the hypothesis that short-term power spectral measures of R-R variability (calculated from 2 to 15 minutes of normal R-R interval data) will predict all-cause mortality or arrhythmic death. Power spectral analyses were performed on the entire 24-hour R-R interval time series. To compare with the 24-hour analyses, short segments of ECG recordings were selected for analysis from two time periods—8 AM to 4 PM, and 12 midnight to 5 AM. The former corresponds to the time interval during which short-term measures of R-R variability would most likely be obtained. The latter, during sleep, represents a period of increased vagal tone, which may simulate the conditions that exist when patients have a signal-averaged ECG recorded—that is, lying quietly in the laboratory. Four frequency domain measures were calculated from spectral analysis of R-R intervals over a 24-hour period. The 24-hour power spectral density was computed, and the power within three frequency bands was calculated: (1) VLF power, (2) LF power, and (3) HF power. In addition, the ratio of LF to HF power was calculated. These measures were calculated for 15-, 10-, 5-, and 2-minute segments during the day and at night. Mean power spectral values from short periods during the day and night were similar to 24-hour values, and the correlations between short segment values and 24-hour values were strong (most correlations were ≥0.75). Using the optimal cut points determined previously for the 24-hour power spectral values, the survival experience of patients with low values for R-R variability in short segments of ECG recordings was compared with that with high values. Power spectral measures of R-R variability were excellent predictors of all-cause, cardiac, and arrhythmic mortality, as well as sudden death. Patients with low values were two to four times as likely to die during an average follow-up of 31 months as were patients with high values. Thus, excellent prediction of postinfarction mortality can be made using power spectral analysis of a 5-minute segment of ECG recording.

R-R Variability Index to Predict Arrhythmic Events After Myocardial Infarction

Farrell et al.[48] studied the ability of the R-R variability index to predict arrhythmic events (sustained ventricular arrhythmias or arrhythmic death) in 416 patients with acute myocardial infarction. During an average follow-up of 20 months, 24 arrhythmic events and 47 deaths occurred in the study group. A 24-hour ECG and a signal-averaged ECG were performed 6 or 7 days after myocardial infarction. R-R variability was quantified by triangular interpolation of the frequency distribution of R-R interval durations (the R-R variability index). This index is a measure of low frequency oscillations of R-R intervals and is strongly associated with ultra-LF power or the SDANN index. The mean value for R-R variability index was 27 ± 11 msec (range, 3–81 msec). Farrell et al. arbitrarily chose a value of 20 msec for R-R variability index to divide their group into 113 patients (27%) with low values and 348 patients (73%) with high values. The risk of experiencing an arrhythmic event during 2 years of follow-up was 32 times as high in the group with an R-R variability index below 20 msec as in the group with a value of 20 msec or larger. The risk of experiencing a cardiac death was about seven times as high in the group with an R-R variability index below 20 msec. The R-R variability index was a stronger univariate predictor of arrhythmic events or cardiac death than were ventricular arrhythmias, signal-averaged ECG, ejection fraction, exercise test, and coronary angiography. R-R variability index did not predict recurrent myocardial infarction. Figure 101–7 shows how combinations of risk predictors improve positive predictive accuracy for arrhythmic events during long-term follow-up after myocardial infarction. Adding the signal-averaged ECG to the R-R variability index doubled positive predictive accuracy, and adding repetitive ventricular premature complexes to the combina-

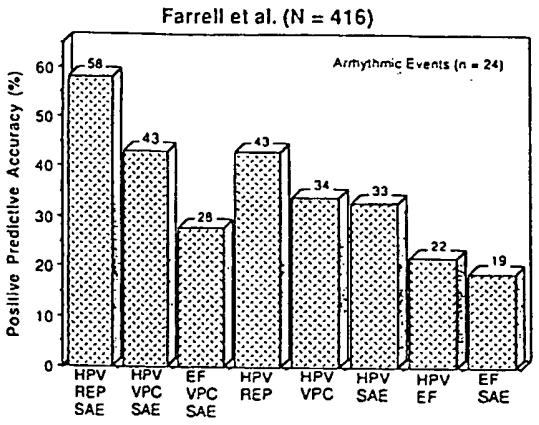

Figure 101–7. Improving positive predictive accuracy using combinations of risk predictors after myocardial infarction. Although each risk predictor has modest (<20%) positive predictive accuracy for arrhythmic events when used alone, the positive predictive accuracy is 40% to 60% for some of the combinations. EF, Left ventricular ejection fraction; HPV, heart period variability index; REP, repetitive ventricular premature complexes; SAE, signal-average ECG; and VPC, ventricular premature complexes. (From Bigger JT Jr, Rottman JN: *In* Podrid PJ, Kowey PR [eds]: Cardiac Arrhythmias, Chapter 19. Baltimore, Williams & Wilkins [In press].)

tion almost doubled it again. The best multivariate predictor for arrhythmic events was the combination of three variables: (1) R-R variability index below 20 msec, (2) a positive signal-averaged ECG, and (3) repetitive ventricular premature complexes present in the same 24-hour ECG recording that was used to calculate R-R variability. The combination of these three variables had a positive predictive accuracy of 58%.[48]

The study of Farrell et al.[48] suggests that measures of R-R variability predict arrhythmic events better than non-arrhythmic deaths or recurrent ischemic events. Also, they showed that combinations of non-invasive variables could achieve positive predictive accuracies in the 50% range.

Effect of Myocardial Infarction on R-R Variability

Bigger et al.[49] showed that measures of R-R variability are reduced to about 25% of normal 2 to 3 weeks after myocardial infarction. It is not known whether R-R variability is reduced prior to myocardial infarction in patients with coronary heart disease. It is known that experimental myocardial infarction created in dogs by coronary artery ligation is followed by an abrupt decrease in R-R variability.[12] Several small studies have studied the recovery of R-R variability after myocardial infarction. Both early and late phases of recovery have been studied.

Early Phase of Recovery. Flapan et al.[50] studied 20 highly selected patients to define the time course of recovery of vagal modulation R-R intervals after a first myocardial infarction. Cardiac parasympathetic activity was estimated using counts of the number of times that successive R-R intervals differed by more than 50 msec (NN50) in a 24-hour period. The NN50 is strongly correlated with HF power. This study excluded patients with previous infarction, age over 70 years, history of diabetes, renal failure, alcohol abuse, hypertension, and prior treatment with or contraindication to treatment with β-adrenergic blocking drugs or with antihypertensive drugs. Patients with arrhythmias or heart failure on admission to the coronary care unit also were excluded. All patients were treated with streptokinase and aspirin acutely, and they continued to receive atenolol and aspirin during the 3-month follow-up period. Continuous 24-hour ECG recordings were made at 1.5, 7, 42, and 140 days after myocardial infarction. For the 20 patients overall, NN50 doubled between 1.5 days and 42 days after infarction and tripled between 1.5 days and 140 days. Figure 101–8 shows that a striking difference in the pattern of recovery of NN50 was found depending on the site of infarction. For the 9 patients with inferior myocardial infarction, NN50 was within normal limits for age at 1.5 days after infarction and did not change significantly during the 140-day follow-up. For the 11 patients with anterior myocardial infarction, NN50 was 20% of normal at 1.5 days and recovered progressively to 67% of normal by 140 days (see Fig. 101–8). By 42 days after myocardial infarction, there was no significant difference in NN50 between patients with anterior and inferior infarcts. In anterior infarcts, there was a striking difference between the time course of recovery of heart rate, which reached stable values by day 7, and the time course of recovery of R-R variability which increased substantially between 42 and 140 days. These workers postulated that stimulation of vagal afferent nerves by ischemia and prostaglandins preserved the efferent vagal activity in inferior myocardial infarction.

The patients in the study by Flapan et al. were highly selected and small in number. Therefore, the study needs to be confirmed and extended before the fascinating findings are considered established. If confirmed, the mechanism for the difference between vagal activity for inferior and anterior myocardial infarction needs further exploration. For inferior myocardial infarcts, Flapan et al. postulated that the infarct process, especially prostaglandin release, causes increased vagal afferent nerve traffic responsible for preserving efferent vagal activity. However, it is not clear why the increase in afferent vagus nerve traffic postulated for inferior infarcts would not increase NN50 above normal values rather than just preserve normal values. Also, their explanation does not account for the marked decrease in cardiac vagal activity in anterior myocardial infarction. Bigger et al. explained the decrease in cardiac vagal activity in anterior infarction by postulating an increase in afferent

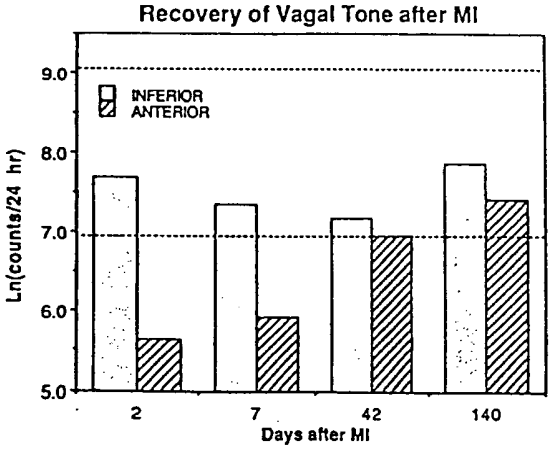

Figure 101–8. Recovery of vagal activity early after myocardial infarction. The natural logarithm of the counts of number of times that successive normal R-R intervals differed by more than 50 msec during a 24-hour period is plotted on the y-axis; time after myocardial infarction (MI) is plotted on the x-axis. In this selected sample of 20 patients, vagal activity decreased markedly in patients with anterior myocardial infarction, but not in those with inferior myocardial infarction. By 42 days after myocardial infarction, the counts had nearly recovered to a stable value. (From Bigger JT Jr, Rottman JN: *In* Podrid PJ, Kowey PR [eds]: Cardiac Arrhythmias, Chapter 19. Baltimore, Williams & Wilkins [In press].)

sympathetic nerve traffic, an effect that has been shown to decrease efferent vagal nerve traffic in experimental myocardial ischemia.[51] We have much more to learn about the precise mechanisms accounting for changes in cardiac neural activity that occur during acute myocardial infarction in humans.

Late Phase of Recovery. Bigger et al.[49] studied recovery of R-R variability in the placebo group in the Cardiac Arrhythmia Pilot Study (CAPS). The 68 placebo-treated patients who had 24-hour ECG recordings at baseline and at 3, 6, and 12 months after myocardial infarction were studied. The 24-hour power spectral density was computed using fast Fourier transforms and divided into four components of the R-R power spectrum—ULF (<0.0033 Hz), VLF (0.0033 to < 0.04 Hz), LF (0.04 to < 0.15 Hz), and HF (0.15–0.40 Hz) power. Total power (power < 0.40 Hz) also was calculated. The mean baseline values (25 days after myocardial infarction) for the five frequency domain measures of R-R variability in the CAPS patients were similar to those found in 715 patients who participated in the Multicenter Post Infarction Program (MPIP), indicating that the CAPS sample is generally representative of postinfarction patients with respect to these measures. Twenty-five days after myocardial infarction, the values for the five measures of R-R variability were one-third to one-half of those found in 95 normal persons of similar age and gender (Table 101–4).

Figure 101–9 shows the time course of recovery of R-R variability during the year after myocardial infarction. There was a substantial increase in all measures of R-R variability between the baseline 24-hour ECG recordings and the 3-month recordings ($p < .001$). Between 3 and 12 months, the values were stable for the group as a whole as well as for individual patients (intraclass correlation coefficients ≥ 0.66). Table 101–4 shows that, even at 12 months after infarction, the average full recovery values for the five measures of R-R variability were only one-half to two-thirds the values found in the sample of 95 normal age- and sex-matched controls. However, during the year after myocardial infarction, some patients recover to normal values of R-R variability whereas others show little recovery or actually decrease.

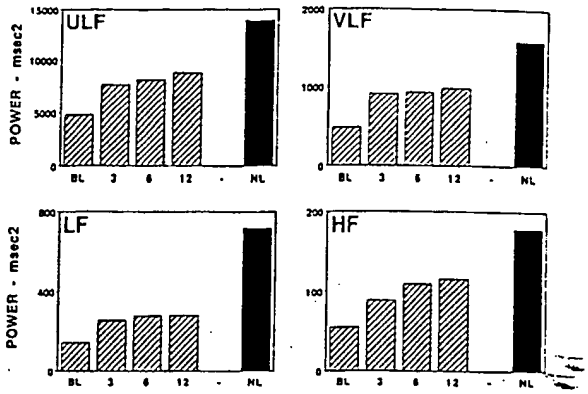

Figure 101–9. Recovery of heart period variability during the year after myocardial infarction. Data are plotted for 68 patients in the placebo group of the Cardiac Arrhythmia Pilot Study who had a complete set of 24-hour ECG recordings. Because the distributions of the frequency domain measures of heart period variability are markedly skewed, the geometric means are plotted for baseline (BL) and 3, 6, and 12 months after myocardial infarction *(striped bars)*. For comparison, the geometric means are plotted for a group of 95 normal (NL) persons of similar age and sex *(black bars)*. On average, recovery was complete by 3 months after infarction. However, average recovery values after infarction do not reach normal. ULF, Ultra low frequency power; VLF, very low frequency power; LF, low frequency power; and HF, high frequency power. (Data from Bigger JT Jr, et al: J Am Coll Cardiol 18:1643–1649, 1991.)

Table 101–4. COMPARISON OF THE BASELINE AND 12-MONTH 24-HOUR ECG RECORDINGS FROM THE CAPS PLACEBO GROUP WITH 24-HOUR ECG RECORDINGS FROM NORMAL SUBJECTS (MEAN ± SD)

Variable	CAPS Baseline* (n = 90)	CAPS 12 Months (n = 82)	Normal Persons (n = 95)
Normal R-R intervals (msec)	780 ± 141	841 ± 120	797 ± 100
ULF power (<0.0033 Hz) (msec²)	6528 ± 5062	10796 ± 6965	16592 ± 10525
Ln ULF power	8.46 ± 0.90	9.07 ± 0.70	9.54 ± 0.61
VLF power (0.0033–0.04 Hz) (msec²)	846 ± 849	1360 ± 1321	1913 ± 1328
Ln VLF power	6.15 ± 1.30	6.89 ± 0.84	7.37 ± 0.60
LF power (0.04–0.15 Hz) (msec²)	302 ± 472	504 ± 660	913 ± 719
Ln LF power	4.89 ± 1.42	5.65 ± 1.14	6.58 ± 0.70
HF power (0.15–0.40 Hz) (msec²)	116 ± 230	216 ± 305	291 ± 454
Ln HF power	3.97 ± 1.25	4.74 ± 1.12	5.19 ± 0.88
Total power (<0.40 Hz) (msec²)	7793 ± 594	12877 ± 8187	19710 ± 12248
Ln total power	8.63 ± 0.92	9.25 ± 0.69	9.72 ± 0.58

CAPS, Cardiac Arrhythmia Pilot Study; Ln, natural logarithm; LF, low frequency; HF, high frequency; ULF, ultra low frequency; VLF, very low frequency.

*The baseline recordings were made 25 ± 17 days after myocardial infarction. The normal persons were matched for age and sex with the patients with previous myocardial infarction. The power spectral values were compared for CAPS baseline and 12-month ECG recordings and for CAPS 12-month recordings and the recordings made in normal persons. Both comparisons showed statistically significant differences.

From Bigger JT Jr, et al: J Am Coll Cardiol 18:1643–1649; 1991. Reprinted with permission from the American College of Cardiology.

Predictive Value of Power Spectral Measures of R-R Variability Late After Myocardial Infarction

To determine whether power spectral measures of R-R variability predict death when measured late after infarction (i.e., after full recovery), Bigger et al.[32] studied the 331 patients in the CAPS who survived for 1 year, had 24-hour ECG recordings made after the CAPS drug was washed out, and were discharged on no antiarrhythmic drug therapy. Thirty deaths occurred in the CAPS group between 1 and 2.2 years after myocardial infarction. Periodograms were calculated using 24-hour continuous ECG recordings, and six power spectral measures of R-R variability were calculated: ULF, VLF, LF, HF, and total power and the LF/HF ratio. Because of the increase in R-R variability that takes place after myocardial infarction, the optimal cutpoints for measures of R-R variability in the 1-year recordings were substantially higher than those previously determined for 24-hour ECG recordings made about 2 weeks after infarction (Table 101–5). Each power spectral measure of R-R variability had a strong and significant univariate association with 2.5-year all-cause mortality; the relative risks for these variables ranged from 2.5 to 5.6 (Fig. 101–10).

The prediction of death from the measures of R-R variability made 1 year after myocardial infarction was not improved when measures of R-R variability made within a month of myocardial

Table 101–5. OPTIMAL CUTPOINTS FOR PREDICTION OF ALL-CAUSE MORTALITY AFTER MYOCARDIAL INFARCTION[40, 49] BY FREQUENCY DOMAIN MEASURES OF HEART PERIOD VARIABILITY

Variable	Optimal Cutpoints	
	At Discharge 2 Weeks After MI	*After Recovery From MI*
ULF power ($msec^2$)	1600	5000
VLF power ($msec^2$)	180	600
LF power ($msec^2$)	35	120
HF power ($msec^2$)	20	35
Total power ($msec^2$)	2000	6000
LF/HF ratio	0.95	1.6

HF, high frequency; LF, low frequency; MI, myocardial infarction; ULF, ultra low frequency; VLF, very low frequency.

infarction were added to the survival model.[52] After adjustment for age, NYHA functional class, rales in the coronary care unit, left ventricular ejection fraction, and ventricular arrhythmias, measures of R-R variability still had a strong and significant independent association with all-cause mortality. It is clear from this study that R-R variability, measured after full recovery from myocardial infarction, predicts death independent of other important postinfarction risk predictors. The final recovery values for R-R variability are the best predictors of subsequent events—that is, knowledge of the recovery pattern does not improve prediction significantly.

USE OF R-R VARIABILITY TO STUDY DISEASE PROGRESSION OR DRUG EFFECTS

Factors that Modify R-R Variability in Normal Persons

Age. Variables that reflect HF power (sinus arrhythmia) have been the best studied for their relationship to age. Pagani et al.[21] studied 57 apparently normal persons; 30 were 20 to 30 years of age, 10 were 30 to 45 years of age, and 17 were 45 to 60 years of age. The gender of the subjects was not reported. Total R-R variance in a series of 512 R-R intervals decreased with age from age 20 to 60; the decline was steeper between ages 20 and 40 than between ages 40 and 60.[20] Shannon et al.[53] studied 33 apparently normal men, aged 31 ± 16 years (range, 9 to 62 years), using power spectral analysis of instantaneous heart rate. Subjects matched their breathing to a metronome frequency of 0.25 Hz to separate LF from HF power. Heart rate data were acquired in 256-second segments in the supine and in standing positions. For HF power in the supine position, there was a marked decline over the age range 9 to 28 years and very little decrease from age 30 to 62 years; an exponential model fit these data better than a linear model. The values for HF power in the standing position were about 60% of those in the supine position, but the regression of HF power on age was similar. The decline of LF power with age was linear from age 9 to 62 years, especially in the standing position. Shannon et al.[53] concluded that the influence of cardiac vagal and sympathetic nervous activity declines at significantly different rates with aging. They speculated that other studies that showed a linear relationship between HF oscillations of R-R intervals or instantaneous heart rate and age were confounded by admixing vagal and sympathetic signals and failing to take account of posture. Schwartz et al.[54] studied 56 healthy men (n = 38) and women (n = 18) aged 20 to 81 who were classified as young (ages 20 to 39), middle-aged (ages 40 to 59), and elderly (ages 60 to 81). They used power spectral analysis of R-R variability in 5-minute segments of ECG to evaluate changes in autonomic activity as a function of age. They found no relationship between heart rate and age in resting supine subjects. Both HF and LF power showed a modest decline with increasing age, but the LF/HF ratio did not change with age in either the supine or standing position (Fig. 101–11).

Molgaard et al.[55] obtained one 24-hour Holter ECG recording in 140 apparently healthy subjects, 51 women and 89 men with a mean age of 53 years (range, 40 to 77 years). They calculated the SDNN over 24 hours and two strongly related time domain measures of cardiac vagal activity, pNN50 and pNN6% (the fraction of adjacent normal R-R intervals that differ by more than 6%); these authors called pNN6% the parasympathetic activity index. There

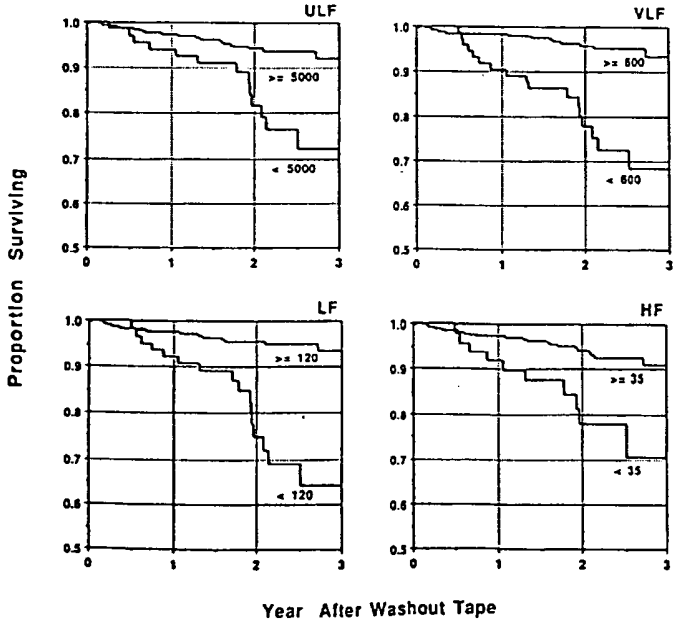

Figure 101–10. R-R variability measured late (1 year) after myocardial infarction predicts death during the following 3 years. Kaplan-Meier survival curves are plotted for 331 patients in the high or low category (optimal cut points) for the four mutually exclusive frequency domain measures of heart period variability, ULF, VLF, LF, and HF power, using all-cause mortality as the end point. (From Bigger JT Jr, et al: J Am Coll Cardiol 21:729–736, 1993. Reprinted with permission from the American College of Cardiology.)

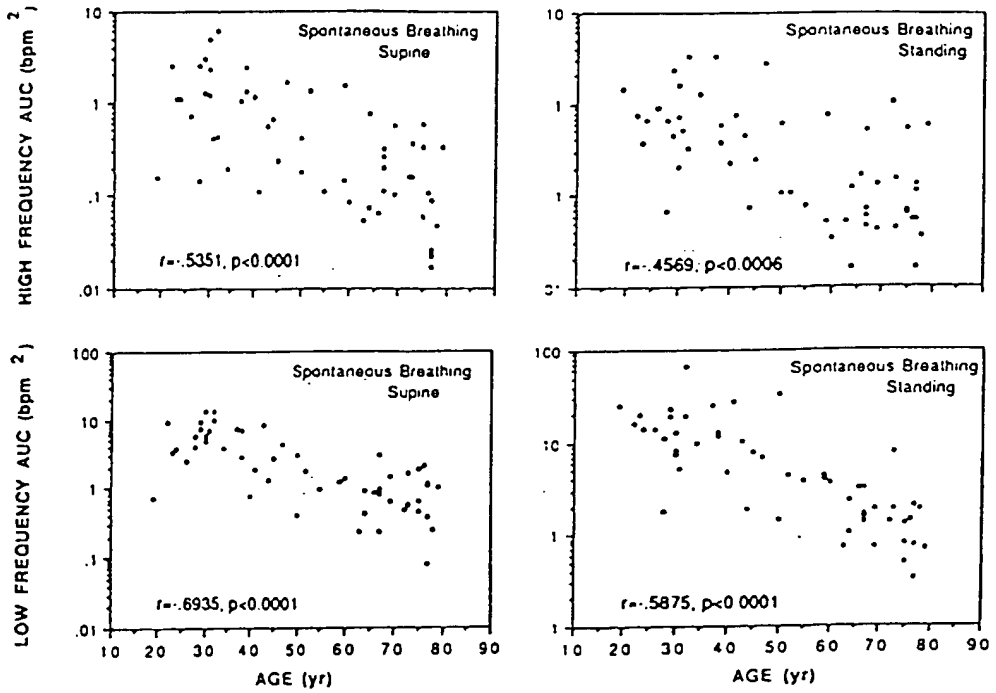

Figure 101–11. High and low frequency power are inversely related to age. The sample comprised 38 normal men and 18 normal women, aged 20 to 81 years. Five minutes of R-R interval data were recorded in the supine position and five minutes were recorded in the standing position. Instantaneous heart rate was converted to the frequency domain using the fast Fourier transformation. The x-axis is age in years. Power is plotted on the y-axis on a log scale. Low frequency power is defined as the area under the curve (AUC) from 0.04 to 0.12 Hz, and high frequency power is defined as the area under the curve from 0.24 to 0.32 Hz. (From Schwartz JB, et al: J Gerontol 46:M99–M116, 1991.)

was a substantial decrease in pNN6% with increasing age, which they attributed to decreased efferent vagal activity with age combined with decreased responsiveness of the sinus node to autonomic activity in the elderly. Ewing et al.[36] studied 77 normal persons, 57 men aged 18 to 65 years and 20 women aged 18 to 57 years, using NN50 to assess cardiac parasympathetic activity. They found an inverse correlation between age and 24-hour NN50 ($r = -0.55$).

Sex. At any age, there is a trend for men to have higher values for HF power or other measures of cardiac vagal activity than women, but the trend is not significant.[36]

Physical Fitness. Goldsmith[37] compared 24-hour cardiac parasympathetic activity for eight aerobically trained men (aged 29 ± 4 years) with eight untrained men (aged 29 ± 3 years). The two groups were closely matched on age, height, weight, and body mass. However, the oxygen consumption during maximal bicycle exercise (Vo_2) differed substantially—67 ± 4 ml/kg/min for the aerobically trained men versus 36 ± 5 ml/kg/min for the untrained men. The average R-R interval was substantially higher in the trained men (1101 ± 146) compared with the untrained men (747 ± 61) ($p < .0005$). HF power was four times greater in trained men than in untrained men (Fig. 101–12). Also, HF power represented a larger fraction of the total power in the R-R power spectrum for trained men compared with untrained men (3.0% versus 1.3%). Goldsmith et al.[38] studied 37 normal subjects, 33 men and 4 women aged 30 ± 5 years (range, 22 to 44 years), to evaluate the relationship between Vo_2 and three measures of cardiac vagal activity: HF power in the R-R power spectrum, r-MSSD, and pNN50. The Vo_2 ranged from 25 to 70 ml/kg/min. The correlation between Vo_2 and the three measures of cardiac vagal activity were all above 0.70, and the relationship remained strong after adjusting for age. These studies showed convincingly that endurance-trained men exhibit greater cardiac parasympathetic activity than untrained men during sleep and while awake. This effect explains a large part of the resting bradycardia of athletes but is not the only responsible factor. Previous studies have uniformly shown that the intrinsic heart rate contributes significantly to resting bradycardia in athletes. Also, physical fitness accounts for more than 50% of the variance in measures of cardiac vagal activity in a group of normal subjects. These authors suggested that exercise could improve cardiovascular morbidity and death by increasing cardiac vagal activity.[37] Molgaard et al.[39] found that physical training was the factor with the strongest association with a high parasympathetic activity index during both day and night.

Miscellaneous. Hayano et al.[39] studied the short-term effects of cigarette smoking in nine normal men aged 24 to 30 years and found that the average R-R interval and HF power decreased for about 10 minutes after smoking a cigarette. These authors also compared short-term measures of R-R variability in 81 male volunteers aged 19 to 52 years. They found that HF power but not LF power was decreased in young (<30 years of age) heavy cigarette smokers. Also, the decrease in HF power that usually occurs on standing was blunted in young heavy cigarette smokers. Molgaard et al.[39] found that a measure of cardiac vagal activity, pNN6%, was decreased in smokers, but only during the day.

Day-to-Day Stability of Power Spectral Measures of R-R Variability In Normal Subjects

Previously studied Holter variables, such as ventricular arrhythmias or episodes of ST depression, are variable from day to day. It

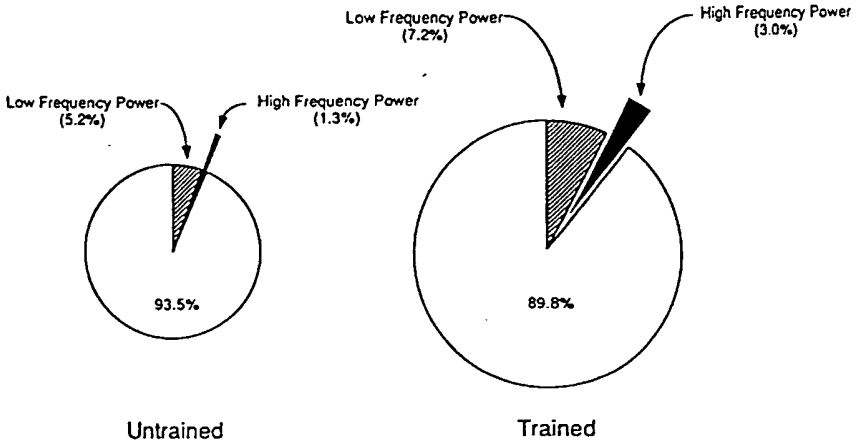

Figure 101–12. The relative contribution of low frequency (0.04–0.15 Hz) and high frequency (0.15–0.40 Hz) power to the 24-hour total power in trained and untrained subjects. The area of the circles is proportional to total power. The majority of the 24-hour total power is from frequencies <0.04 Hz in both groups. The proportional contribution of high frequency power to total power is significantly greater in the trained group. (From Goldsmith R, et al: J Am Coll Cardiol 20:552–558, 1992. Reprinted with permission from the American College of Cardiology.)

might be anticipated that there would be considerable day-to-day instability in measures of R-R variability as well, particularly those components that reflect sympathetic or parasympathetic nervous activity. Kleiger et al.[40] studied 14 normal subjects 20 to 55 years of age to determine day-to-day stability of R-R variability. Two 24-hour recordings were made 3 to 65 days apart (median, 18 days), one during no treatment and the other during placebo treatment in a crossover drug study that included atenolol and diltiazem as the other two treatments. Figure 101–13 shows data for each of the 288 5-minute periods for two 24-hour ECG recordings made 16 days apart in a normal subject. The day–night differences for R-R interval, LF power, HF power, and LF/HF ratio are large, and three- to four-fold changes in R-R variability are evident between 5-minute segments in the same hour. Nevertheless, the mean values for LF and HF power were virtually identical in the two 24-hour ECG recordings. Furthermore, the intraclass correlation coefficients (a measure of within-subject agreement) for the 14 normal subjects were 0.91 and 0.84 for LF and HF power, respectively. The sample was divided at the median time between recordings, and it was found that the intraclass correlation coefficients were 0.93 and 0.90

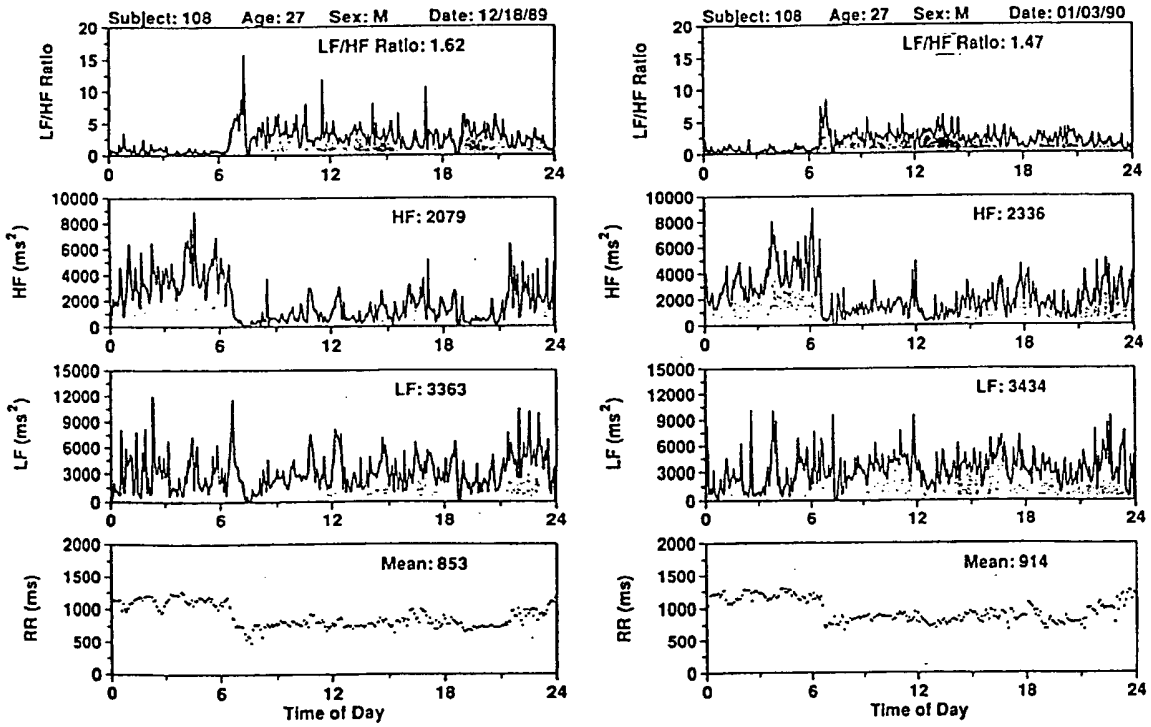

Figure 101–13. The day-to-day stability of R-R variability. The subject was a normal 27-year-old man. The two panels plot R-R interval, LF power, HF power, and LF/HF ratio for two 24-hour ECG recordings made 16 days apart. Not only are the 24-hour average values similar for the two recordings, but also the profile of changes from 5 minutes to 5 minutes during the day and night are remarkably similar.

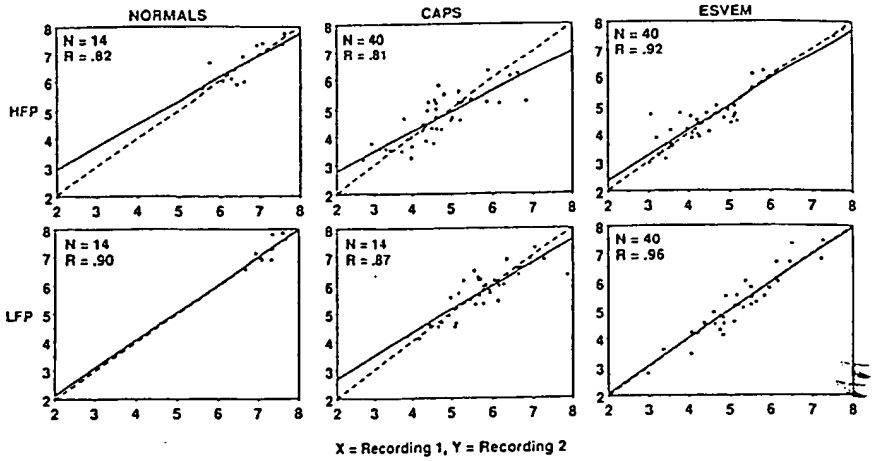

Figure 101–14. The day-to-day stability of R-R variability. The natural logarithms of high frequency power (HFP) and low frequency power (LFP) are plotted for three groups: a group of normal subjects *(left)*; the Cardiac Arrhythmia Pilot Study (CAPS) group *(middle)*; and the Electrophysiologic Studies Versus Electrocardiographic Monitoring (ESVEM) group *(right)*. The subjects are ranked for severity of cardiac disease from left to right (none, moderate, severe). The logarithms of the values for high frequency power in the first 24-hour ECG recording are plotted on the x-axis, and those for the second 24-hour ECG recording are plotted on the y-axis. The diagonal solid lines are the lines of identity (slope = 1, intercept = 0); if the values for day 1 and day 2 were identical, they would lie on this line. The diagonal dashed lines are the linear regression lines calculated for the data. The agreement between paired recordings is excellent for all three groups. (Plotted from data in Bigger JT Jr, et al: Am J Cardiol 69:718–723, 1992.)

for LF and HF power in recordings made less than 18 days apart and 0.88 and 0.75 in recordings made 18 or more days apart. Also, the standard errors of measurement between the two recordings was very small.

Power spectral measures of R-R variability, averaged across a 24-hour period, were essentially constant from day to day during the range of time studied (3 to 65 days) (Fig. 101–14). This remarkable day-to-day stability exists for the 24-hour average values for power spectral measures of R-R variability despite marked differences among the 5-minute intervals during a day. The excellent day-to-day stability of R-R variability over 24 hours makes it easy to detect small differences in power spectral measures of R-R variability due to disease or to drug treatment. The study of Kleiger et al.[60] also showed a lack of any "placebo effect". The subjects in their study were blinded as to treatment but knew they were taking placebo, atenolol, or diltiazem. Even so, there were no differences between the values for R-R variability measured during placebo treatment and those found in the baseline tape when subjects were not taking any treatment. In other studies, a significant "placebo effect" was found for blood pressure and for frequency of angina pectoris in placebo-controlled studies of antihypertensive or antianginal drugs. It is surprising that no placebo effect was found for measures of R-R variability that reflect sympathetic and parasympathetic nervous activity and are responsive to mental stress.

Stability of Power Spectral Measures of R-R Variability in Patients with Cardiac Arrhythmias

Bigger et al.[61] studied the day-to-day stability of R-R variability in patients with coronary heart disease, previous myocardial infarction, left ventricular dysfunction, and ventricular arrhythmias. Two groups were studied—those with unsustained, prognostically significant ventricular arrhythmias and those with sustained ventricular arrhythmias. The sample selected to study unsustained ventricular arrhythmias was a random sample of 40 patients in the placebo group of the CAPS. The sample selected to study sustained ventricular arrhythmias was a random sample of 40 patients in the ESVEM study. The ESVEM group was much sicker than the CAPS group in terms of functional class (class II–IV, 84% versus 5%), average left ventricular ejection fraction (0.34 ± 0.16 versus 0.46 ± 0.12), and median ventricular arrhythmia frequency (125/hour versus 18/hour). Total power and each of its components were lower in the ESVEM group than in the CAPS group. However, the difference between these two groups of patients was especially large for total power and ULF power; the values in the ESVEM group were 51% and 56% of the values in the CAPS group ($p < .001$ by independent sample t-tests). The difference between the ESVEM and CAPS groups was much smaller for VLF, LF, and HF power, where the values in the ESVEM group were 78%, 90%, and 80% of those found in the CAPS group ($p < .01$, $p < .05$, and p = ns, respectively, by independent sample t-tests).

There were no significant differences in measures of R-R variability between the two 24-hour recording sessions in either the ESVEM or the CAPS group (see Fig. 101–14). Remarkably, the two sets of mean values for the two recordings were almost identical within the ESVEM and the CAPS groups. Graphical examples of the paired measures for LF and HF power are given in Figure 101–14. The agreement between the two 24-hour recordings is evident. Also, the graphs show that the agreement of paired measurements is better in the ESVEM group than in the CAPS group—the regression lines are closer to the lines of identity and the correlation coefficients are larger. The intraclass correlation coefficients for LF or HF power in the paired recordings were 0.87 and 0.80 for the CAPS group and 0.96 and 0.92 for the ESVEM group, indicating excellent within-subject agreement between the paired measurements.

The study by Bigger et al.[61] showed that the reproducibility of R-R variability measurements in patients with previous myocardial infarction and ventricular arrhythmias is comparable to the high day-to-day stability previously found by Kleiger et al. in a smaller group of normal subjects. The stability of measures of R-R variability facilitates distinguishing real changes due to progression or regression of cardiac disease or those due to drug effects from apparent changes due to random variation.

Drugs Acting on the Cholinergic Receptor

Effects of Cholinergic Blockade on Power Spectral Measures of Vagal Activity. Pomeranz et al.[20] studied eight normal men aged 22 to 36 years and showed that 0.03 mg/kg of atropine abolished HF power and markedly attenuated LF power in 256-second heart rate power spectra. These findings indicate clearly that parasympathetic modulation of R-R intervals is totally responsible for HF

power and dominates LF power in supine normal subjects. Many drugs have anticholinergic actions (e.g., antihistamines and tricyclic antidepressant drugs); these drugs decrease HF power substantially, similar to atropine. Figure 101–15 shows the effect of a tricyclic antidepressant drug, desipramine, on R-R interval, HF power, LF power, and LF/HF ratio over a 24-hour interval. The marked effect on HF power indicates a substantial decrease in cardiac vagal activity.

Effects of Cholinergic Activation on Power Spectral Measures of Vagal Activity. Low doses of atropine cause transient bradycardia[62] and increase vagal modulation of R-R intervals (increase HF power) by means of a central vagotonic action.[63] Also, low doses of scopolamine, a lipophilic muscarinic blocking agent, increase efferent cardiac vagal activity substantially without significant peripheral blocking effect. Dibner-Dunlap et al.[64] studied 14 normal male subjects aged 27 ± 7 years to determine the effects of scopolamine on R-R intervals, the standard deviation of R-R intervals over a 1-hour period, and the baroreflex sensitivity assessed by graded neck suction. The average R-R interval increased 13% ($p < .001$), and the standard deviation of the R-R interval over a 1-hour period increased 31% ($p < .002$). Also, the abrupt increases in R-R interval caused by stimulating the carotid baroreceptor with anterior neck suction were substantially increased. No changes occurred during treatment with placebo patches. These workers speculated that transdermal scopolamine might improve the prognosis of selected high-risk postinfarction patients by increasing cardiac vagal activity and preventing lethal arrhythmias.

Vybiral et al.[65] studied 32 normal subjects, 4 women and 28 men aged 33 ± 7 years, in the supine position in a quiet room before and 24 hours after application of a transdermal scopolamine patch. Subjects breathed on cue from a metronome signal at 15 breaths per minute for a 10-minute interval while R-R interval data were continuously recorded. HF and LF power were calculated from 128 consecutive R-R intervals. The data were peculiar in that HF power was greater than LF power, but the ratio of the values for HF power before and during scopolamine treatment probably give a qualitative view of the direction and magnitude of drug effect. HF power increased 2.5-fold during scopolamine treatment. Eighty-four per cent of the subjects had minor adverse effects, but only one subject removed the scopolamine patch (after 2 hours) because of adverse effects. Vybiral et al.[65] concluded that transdermal scopolamine increased cardiac vagal activity and speculated that scopolamine might benefit certain patients with myocardial infarction, heart failure, or ventricular arrhythmias.

Effects of Transdermal Scopolamine on Cardiac Vagal Activity after Myocardial Infarction. Casadei et al.[66] studied 36 patients, 4 women and 32 men aged 60 ± 4 years, 4 days after acute myocardial infarction. The patients were randomly assigned to receive a transdermal scopolamine patch (which released about 500 μg over 72 hours) or a placebo patch. R-R variability and baroreflex sensitivity were measured before and 24 hours after the patch was applied. Patients with diabetes mellitus, prostatism, family histories of glaucoma, atrial fibrillation, frequent ventricular premature complexes (>1%), cardiac conduction abnormalities, or liver or kidney disease were excluded. Data for R-R variability were collected at the bedside with the patient in a semirecumbent position; care was

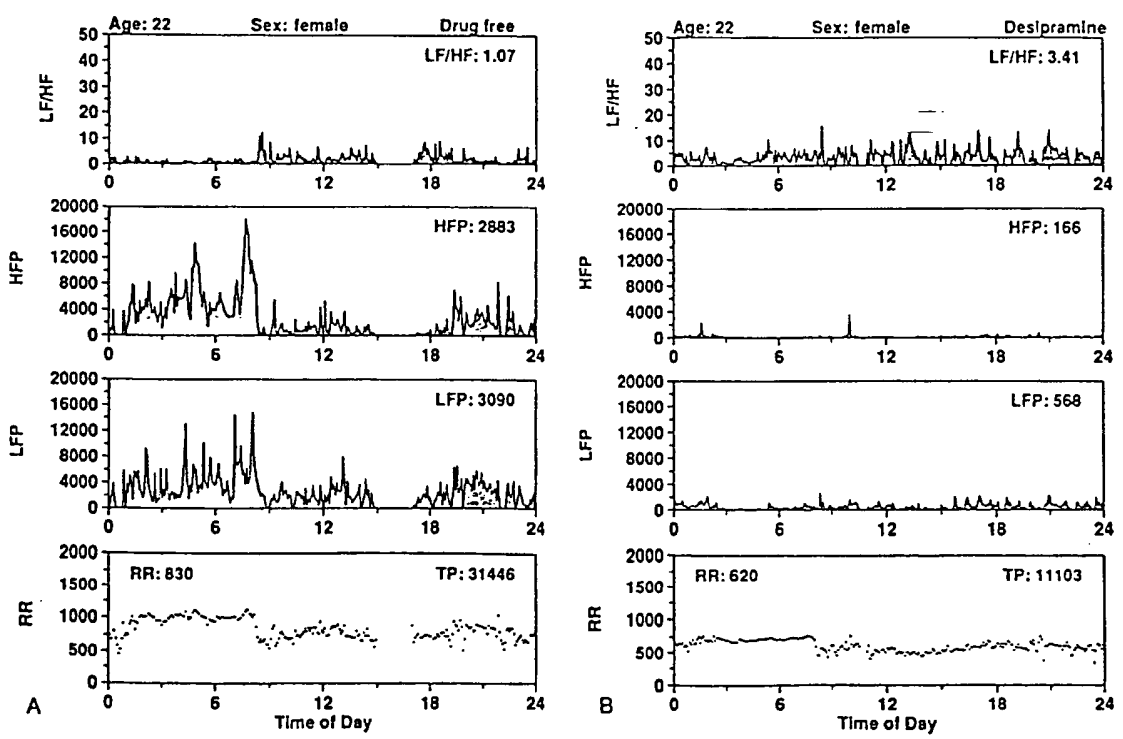

Figure 101–15. The peripheral anticholinergic effect of desipramine causes a marked decrease in vagal modulation of R-R intervals. *A*, Data from a normal 22-year-old woman during placebo treatment. *B*, Data from the same subject during treatment with desipramine. In each panel, the R-R interval and the measures of R-R variability are plotted for each of the 288 5-minute periods during the 24-hour period. During the placebo period, HF power is greater at night and LF/HF ratio is greater during the day. Note the decrease in R-R interval (25%), HF power (94%), and LF power (82%) and the increase (69%) in LF/HF ratio during desipramine treatment. The marked decrease in HF power indicates decreased vagal modulation of R-R intervals. The increase in LF/HF ratio indicates a shift in autonomic balance to sympathetic dominance.

taken to avoid noise or interruption. A series of 512 consecutive R-R intervals was used to calculate time domain measures of R-R variability, and autoregressive methods were used to calculate absolute LF and HF power in units of msec^2.[26] Baroreflex sensitivity was measured by the phenylephrine injection method. In the placebo group (n = 19), average R-R interval, baroreflex sensitivity, and power spectral measures did not change. In the scopolamine group, baroreflex sensitivity increased from 7.1 ± 1.21 to 14.0 ± 2.33 ($p < .05$); the average R-R interval for 512 complexes increased from 794 ± 48.5 to 901 ± 62.7. LF power increased from 73 ± 24.4 to 127 ± 44.3 ($p < .05$), and HF power increased from 63 ± 21.5 to 294 ± 97.0 ($p < .05$). Low-dose scopolamine caused a substantial and sustained increase in baroreflex sensitivity and R-R variability 5 days after myocardial infarction. The 1-day of treatment with low-dose scopolamine was well tolerated. Given the protective effects of cardiac vagal activity that were discussed in a previous section of this chapter, the changes produced by transdermal scopolamine are expected to improve prognosis after myocardial infarction by protecting them from life-threatening cardiac arrhythmias. Before scopolamine therapy can be recommended after myocardial infarction, efficacy and safety needs to be established. It needs to be established that the vagomimetic effect of scopolamine is sustained during long-term treatment and that long-term treatment is well tolerated. Finally, scopolamine therapy must be proved effective and safe in large-scale randomized clinical trials. As Casadei et al.[67] point out, the Cardiac Arrhythmia Suppression Trial showed us that reversing prognostic indicators does not necessarily result in reduced mortality.

Effects of Transdermal Scopolamine on Cardiac Vagal Activity in Patients with Heart Failure. A preliminary report of a study performed in 14 patients with heart failure after myocardial infarction showed that HF power, determined from spectral analysis of 10-minute ECG recordings, increased 44% ($p < .01$) during treatment with transdermal scopolamine.[68] The 24-hour average R-R interval increased by only 5% ($p < .05$). Time domain measures of cardiac vagal activity, r-MSSD and pNN50, were calculated for 24 hours of R-R data and increased by 34% and 73%, respectively ($p < .01$).

β-Adrenergic Blocking Drugs

Effects of Atenolol on Vagal Activity in Normal Subjects. Cook et al.[69] performed a randomized, three-period, placebo-controlled study with a Latin square crossover design to determine the effect of atenolol and diltiazem on time and frequency domain measures of R-R variability calculated from 24-hour continuous ECG recordings. Eighteen normal volunteers, 4 women, and 14 men aged 32 ± 7 years, were given atenolol, diltiazem, and placebo orally in random order. After 7 days of treatment with atenolol, 50 mg four times a day, the 24-hour average normal R-R interval increased 24% ($p < .001$). The three measures of vagal modulation of R-R intervals all increased significantly ($p < .001$) during atenolol treatment: successive normal R-R intervals above 50 msec, 69%; root mean square successive difference of normal R-R intervals, 61%; and HF power in the heart period power spectrum, 84%. LF power increased 45% ($p < .01$), indicating that this variable also reflects vagal modulation of R-R intervals under some conditions. Figure 101–16 shows the effects of atenolol on R-R variability during a 24-hour period.

Effects of Pindolol and Labetalol on Vagal Activity in Normal Subjects. Stein et al.[70] also used a three-period crossover design to compare pindolol, labetalol, and placebo in 10 normal subjects. Pindolol, a β-adrenergic blocking drug with intrinsic sympathomimetic activity, given orally in a dose of 5 mg twice a day, decreased 24-hour average LF and HF power. Labetalol, a drug with combined α- and β-adrenergic blocking activity, given orally in a dose of 100 mg twice a day, caused no significant change in 24-hour average LF or HF power.

Acute Effect of Intravenous Propranolol on Vagal Activity in Normal Subjects. Pagani et al.[21] studied the effect of acute β-blockade in 10 normal subjects aged 20 to 30 years. HF power was calculated from 512 consecutive normal R-R intervals using a hypothesis-driven, parametric estimation technique that "forces" LF power to decrease if HF power increases.[37] A day or so after the baseline measurements, 0.2 mg/kg of propranolol was injected intravenously and power spectra were repeated. During acute β-adrenergic blockade, the average R-R interval increased 29% ($p < .05$) and the absolute HF power increased 174% ($p < .05$). Expressed as "normalized units," HF power increased 36%. Hayano et al.[71] studied the effect of acute β blockade in 15 normal men aged 21 to 24 years. HF power was measured in a 256-second segment of ECG recorded while the subjects rested in the supine position. After the baseline measurement, 0.2 mg/kg of propranolol was administered intravenously over 10 minutes and HF power was measured two minutes later. Intravenous propranolol produced no significant change in either LF or HF power in this study despite a decrease in heart rate from 65 to 59 bpm.

Effect of Chronic Oral Propranolol on Vagal Activity in Normal Subjects. Pagani et al.[21] studied chronic β blockade with 0.6 mg/kg of propranolol in 12 normal subjects. Power spectra were calculated from 512 R-R intervals recorded with the subjects resting in the supine position. The effects of β blockade on LF and HF power were estimated using a hypothesis-driven, parametric estimation technique that "forces" LF power to decrease if HF power increases.[37] They found that propranolol caused a doubling of "normalized" HF power and a 33% decrease in "normalized" LF power.

Effect of Chronic Oral Acebutalol on Vagal Activity in Patients with Heart Failure. Coumel et al.[72] studied the effects of a 10 mg/kg dose of acebutalol, a cardioselective β-adrenergic blocking drug with mild intrinsic sympathomimetic activity, in 30 men and 11 women aged 57 ± 5.7 years. The subjects were 15 normal patients, aged 56 ± 5.8 years; 13 patients with left ventricular hypertrophy, aged 56 ± 7.8 years; and 13 patients with heart failure, aged 61 ± 3.6 years. They found that both HF and LF oscillations of R-R interval decreased during acebutalol treatment and that the LF/HF ratio decreased. These findings suggest that cardiac vagal activity did not increase during acebutalol treatment and that cardiac sympathetic activity was reduced. These results are similar to those obtained by Stein et al.[70] using pindolol, another cardioselective β-adrenergic blocking drug with mild intrinsic sympathomimetic activity.

Effect of Chronic Oral Carvedilol on Vagal Activity in Patients with Heart Failure. Parasympathetic nervous activity is reduced in patients with heart failure. Preliminary studies suggest that β-adrenergic blocker therapy improves outcome in patients with heart failure. Goldsmith et al.[73] reported preliminary results of a study designed to test the hypothesis that treatment with carvedilol, a β-adrenergic blocker that is well tolerated in heart failure, will increase parasympathetic nervous activity in patients with heart failure. Ten patients with chronic heart failure, eight men and two women aged 56 ± 11 years, were treated with 25 mg of carvedilol twice a day. All patients received constant doses of digoxin, diuretics, and angiotensin-converting enzyme inhibitors during the study period. Variables that reflect cardiac vagal activity were calculated from 24-hour ECG recordings made before and 3 to 4 months after starting treatment with carvedilol. Carvedilol markedly increased the measures of cardiac vagal activity—that is, HF power tripled during therapy (Table 101–6). The 24-hour average R-R interval increased substantially and correlated moderately ($r = 0.60$) with the change in LF power. The increases in cardiac vagal activity caused by carvedilol therapy were larger than those seen with other β-adrenergic blocking drugs in normal subjects or patients studied after myocardial infarction. Since low cardiac vagal activity is associated with a high mortality rate after myocardial infarction and since therapy with β-adrenergic blocking drugs improves survival after myocardial infarction, the marked increase in cardiac vagal

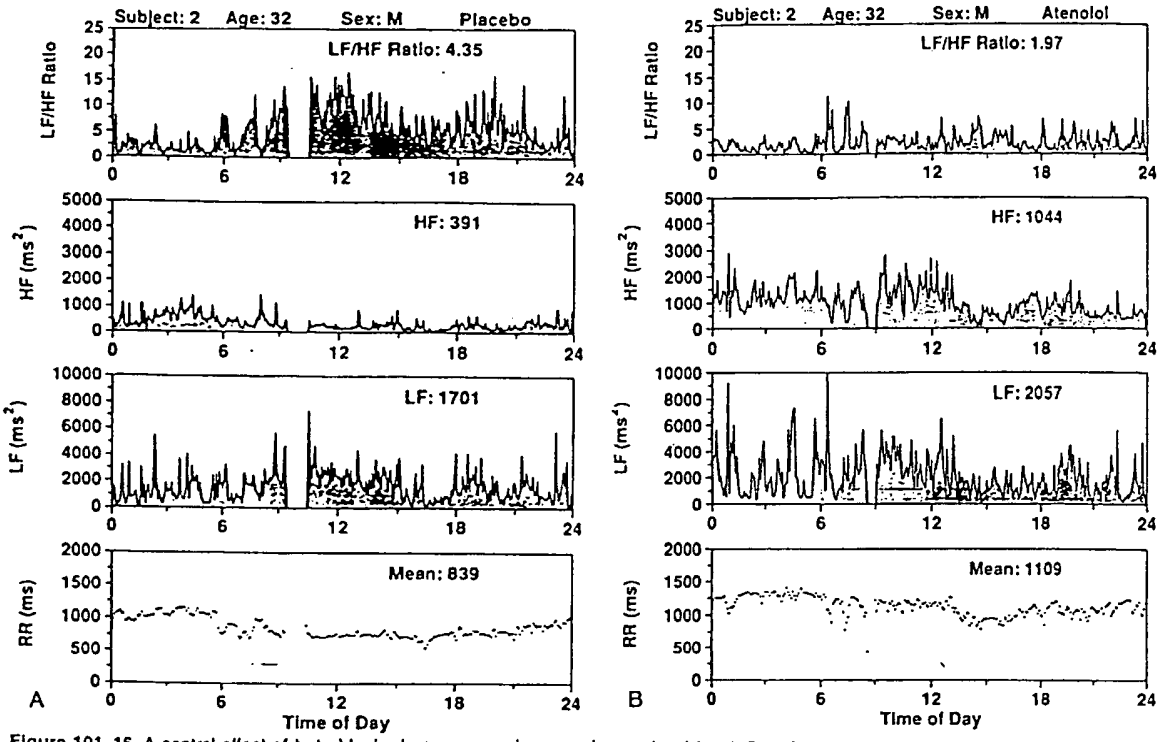

Figure 101–16. A central effect of beta blockade causes an increase in vagal activity. *A*, Data from a normal 32-year-old man during placebo treatment. *B*, Data from the same subject during treatment with atenolol 50 mg four times a day. In each panel, the R-R interval and the measures of R-R variability are calculated and plotted for each of the 288 5-minute periods during the day. During placebo period, HF power is greater at night and LF/HF ratio is greater during the day. Note the increase in R-R interval (32%), HF (167%), and LF power (21%) and the decrease in LF/HF ratio during atenolol treatment. The increase in HF power indicates increased vagal modulation of R-R intervals. The decrease (55%) in LF/HF ratio indicates a decrease in sympathetic modulation of R-R intervals. (From Bigger JT Jr, Rottman JN: *In* Podrid PJ, Kowey PR [eds]: Cardiac Arrhythmias, Chapter 19. Baltimore, Williams & Wilkins [In press].)

activity during carvedilol treatment may have prognostic implications.

Thus, it seems clear that chronic β blockade causes a substantial increase in vagal modulation of R-R variability. The large effect of β blockade on vagal modulation of R-R variability may be masked when the β blocker has other pharmacological properties, such as intrinsic sympathomimetic activity or α-adrenergic blocking activity. The lack of an acute effect of intravenous propranolol on HF power in the study by Hayano et al. is puzzling; it could be that the measurements were made too soon after the drug was injected.

Effects of β-Adrenergic Blocking Drugs on Cardiac Sympathetic Activity. There is little sympathetic nervous activity in resting normal persons.[74] Therefore, the effects of β blockade on sympathetic modulation of R-R intervals in resting normal subjects are variable and small. Pomeranz et al.[20] studied eight normal young men and showed that LF power (0.04–0.12 Hz) increased substantially and HF power (0.22–0.28 Hz) decreased when the subjects stood up. They concluded that LF power reflected a baroreceptor response to blood pressure fluctuations at the same frequency (i.e., Mayer waves). The increase in LF power in the upright position was attributed to either an increased amplitude of LF fluctuations in blood pressure or to an increased gain of the baroreceptor in the upright posture.[75] The increase in LF power in the upright position is due to increased cardiac sympathetic nerve activity as shown by the marked reduction in the standing LF power after β-adrenergic blockade. Similarly, Pagani et al.[21] showed that acute (n = 10 subjects) and chronic (n = 22 subjects) β-adrenergic blockade with propranolol in normal subjects blunted the marked increase in LF power that normally occurs during head-up tilt. Bekheit et al.[76] studied the effects of metoprolol on the response of LF power to head-up tilt after myocardial infarction. Eight patients were studied 2 to 6 weeks after myocardial infarction. Power spectra were calculated using 10 minutes of R-R interval data with the patients supine and 10 minutes of data acquired during head-up tilt. Meto-

Table 101–6. EFFECT OF CARVEDILOL ON CARDIAC VAGAL ACTIVITY IN SEVEN PATIENTS WITH HEART FAILURE

	Geometric Mean (95% Confidence Interval)	
Variable	*Baseline*	*Carvedilol*
24-Hour average R-R interval (msec)	662 (611, 717)	973 (898, 1050)*
HF power (msec²)	33.4 (19.0, 111.3)	100.3 (55.5, 324.9)*
r-MSSD (msec)	5.1 (0, 10.2)	34.6 (29.9, 52.2)*
pNN50 (%)	2.6 (0.3, 4.9)	71.4 (53.8, 89.0)*

*$p < .05$

HF, high frequency.

Reproduced with permission from Goldsmith RL, Krum H, Bigger JT Jr, et al: Beta-blockade increases parasympathetic activity in chronic heart failure. Circulation 88:1103, 1993. Copyright 1993, American Heart Association.

prolol substantially reduced the increase in LF power usually seen during head-up tilt.

Calcium Channel Blocking Drugs

Cook et al.[69] showed that chronic oral diltiazem, 60 mg four times a day, had no significant effect on 24-hour average N-N interval or on any measure of R-R variability in normal subjects. Bekheit et al.[76] found that diltiazem reduced the increase in LF power during head-up tilt to the same degree as metoprolol in nine postinfarction patients. Using the same techniques they found no reduction in the LF power response to head-up tilt during nifedipine treatment.

Digitalis

Effects in Normal Subjects. Kaufman et al.[77] conducted a randomized, three-period, placebo-controlled, crossover study to determine the effect of digoxin, 0.25 mg twice a day, on R-R variability. Twenty normal subjects, ten women and ten men aged 32 ± 9 years, had 24-hour ECG recordings done after 5 days of treatment, and ten subjects (five women and five men aged 30 ± 9 years) had tilt-table studies as well. Figure 101–17 shows the effects of digoxin on R-R variability over a 24-hour interval. The average R-R interval did not change significantly during digoxin treatment, but HF power increased by about 50% and LF power by about 30%. This result suggests that digoxin increased the vagal modulation of R-R intervals without changing the mean value for the R-R intervals. Digoxin had no significant effect on the autonomic response to head-up tilt.

Effects in Patients with Heart Failure. Krum et al.[78] studied the effects of 4 to 8 weeks of oral digoxin treatment on R-R variability in 26 patients with congestive heart failure. The average age was 56 ± 2 years and half of the patients were male. The distribution of NYHA functional class was class I, 6; class II, 11; class III, 9. The average left ventricular ejection fraction for the group was 0.22 ± 0.02. None of the patients had received digoxin treatment before the study and other treatments (e.g., converting enzyme inhibitors or diuretics) were held constant during the study. All patients received digoxin, dosed to maintain the plasma digoxin concentration between 1.0 and 2.5 ng/ml. Patients had 24-hour Holter recordings before and 4 to 8 weeks after digoxin treatment was begun. Before digoxin, HF, LF, and total power were markedly reduced. The 24-hour average R-R interval increased significantly during digoxin treatment. HF power doubled during digoxin treatment, indicating a substantial increase in cardiac vagal activity. The plasma norepinephrine concentration fell significantly during digoxin treatment, suggesting a decrease in sympathetic nervous system activity as well. The LF/HF ratio did not change. These findings taken together suggest that digoxin increased baroreflex sensitivity, which accounts for all of the other findings. The response of patients with moderate congestive heart failure to digoxin was remarkably similar to the response of normal subjects except for the increase in average 24-hour R-R interval seen in patients with heart failure.

Converting Enzyme Inhibitors

Effects in Normal Subjects. Kaufman et al.[77] studied the effects of enalapril, 10 mg twice a day, in the same 20 normal subjects that

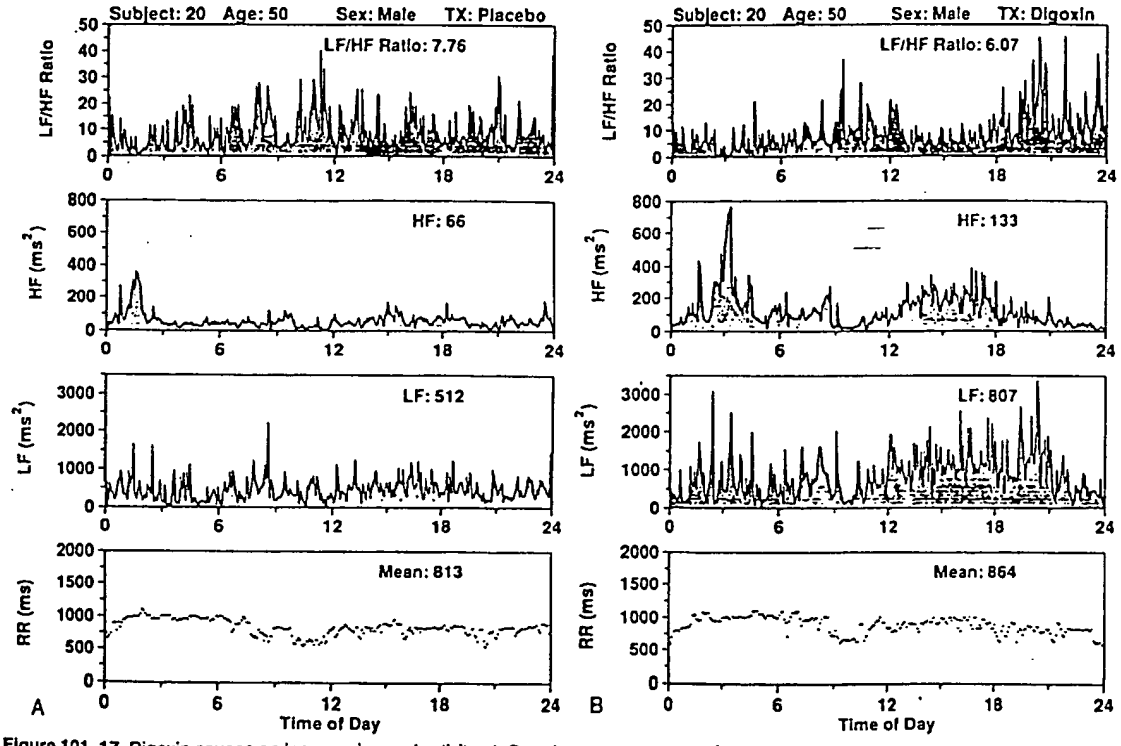

Figure 101–17. Digoxin causes an increase in vagal activity. *A*, Data from a normal 50-year-old man during placebo treatment. *B*, Data from the same subject during treatment with 0.25 mg digoxin twice a day. Digoxin did not cause a significant change in R-R interval. HF and LF power increase and LF/HF ratio decreases during digoxin treatment. The increase in HF power indicates increased vagal modulation of R-R intervals despite the lack of change in the mean value for R-R interval. (From Kaufman ES, et al: Am J Cardiol 72:95–99, 1993.)

were given digoxin. Enalapril had no significant effect on R-R variability or the autonomic response to head-up tilt in normal subjects.

Effects in Patients with Heart Failure. Flapan et al.[79] studied the effect of captopril on vagal modulation of R-R intervals in 32 patients with class III heart failure. All patients were treated in hospital with sodium restriction and diuretics, but none were treated with digitalis glycosides. The mean age of the group was 63 years and the average left ventricular ejection fraction for the group was 0.19 ± 0.06. Twenty of the patients were treated with captopril, 25 mg three times a day, and 12 controls were not given converting enzyme inhibitor therapy. Both groups had two 24-hour ECG recordings done about 4 days apart. Parasympathetic activity was estimated using NN50. There was no difference in NN50 between the two recordings in the control group (median NN50, 340 versus 400). In the captopril group, the median NN50 increased from 482 to 1032 during treatment ($p < .01$), a clear indication of increased cardiac parasympathetic activity. Heart rate did not change during captopril treatment. These authors speculated that captopril might increase parasympathetic activity by reducing angiotensin II levels and thus removing angiotensin's cardiac vagal inhibition. They further speculated that the increase in vagal activity during captopril therapy might contribute to the increased survival seen when heart failure is treated with converting enzyme inhibitors.

Antiarrhythmic Drugs

Cardiac Vagal Activity Decreases During Treatment with Drugs that Have Class I Antiarrhythmic Action. Zuanetti et al.[80] used NN50 to evaluate the effects of three antiarrhythmic drugs on parasympathetic modulation of R-R intervals in a group of patients with cardiac disease being treated for unsustained ventricular arrhythmias. They found that flecainide and propafenone decreased NN50, with a median change of −56% and −64%, while amiodarone did not, with a median change of −8%. They suggested that the substantial decrease of NN50 during class IC antiarrhythmic drug treatment indicated an antivagal effect and speculated that this effect may contribute to the increased mortality rate found for patients treated with this class of antiarrhythmic drugs after myocardial infarction.

Antiarrhythmic Drug-Induced Changes in Cardiac Vagal Activity Do Not Predict Mortality. Following Zuanetti's lead, Bigger et al.[81] tested the hypothesis that antiarrhythmic drugs that decrease R-R variability will predict all-cause mortality during a year of follow-up after myocardial infarction. They compared the effects on R-R variability of encainide and flecainide ($n = 178$ subjects), which increase long-term mortality substantially, with the effects of placebo and moricizine ($n = 177$ subjects), which have no significant effect on mortality during long-term treatment of unsustained ventricular arrhythmias after myocardial infarction. The 24-hour power spectral density was computed from the baseline ECG recordings and drug evaluation tapes, and six frequency domain measures of R-R variability were calculated: ULF (<0.0033 Hz), VLF (0.0033 to <0.04 Hz), LF (0.04 to <0.15 Hz), and HF power (0.15 to <0.40 Hz)—plus total power (<0.40 Hz) and the ratio of LF to HF power. Changes in power spectral measures were related to drug treatment and to mortality. In the placebo group, values for R-R interval and R-R variability increased as a result of recovery from the effects of acute myocardial infarction. Contrasting placebo treatment with all three active antiarrhythmic drug treatments taken together showed that, out of all the measures of R-R variability, only NN50, pNN50, and LF power changed significantly during drug treatment (adjusted $p < .025$); these variables all decreased during drug therapy (62%, 68%, and 16% decreases, respectively). Contrasting encainide and flecainide with moricizine, they found that the encainide and flecainide groups, taken together, produced a larger decrease in LF than moricizine. Survival was significantly worse in the groups treated with encainide and flecainide than in the groups treated with placebo or moricizine (relative risk >2.0, adjusted $p < .05$). The antiarrhythmic drug-induced change in measures of R-R variability was not a significant predictor of all-cause mortality during a year of follow-up after myocardial infarction.

Bigger et al.[81] confirmed Zuanetti's finding that flecainide caused a decrease in NN50 (and other measures of R-R variability) and showed that encainide and moricizine also had this effect—that is, encainide, flecainide, and moricizine all caused a decrease in R-R variability in patients studied about a month after acute myocardial infarction. However, the link between NN50 and mortality postulated by Zuanetti et al. was not found. Encainide and flecainide caused a significant increase in mortality rates; placebo and moricizine did not. Although baseline (predrug) measurements of R-R variability predicted all-cause mortality after myocardial infarction, the decrease in R-R variability produced by the three antiarrhythmic drugs did not predict mortality during follow-up.

Conclusions

For many years, various short-term measures of R-R variability have been used to evaluate the status of the parasympathetic nervous system in diseases such as diabetic neuropathy and for studying the responsiveness of the parasympathetic nervous system in laboratory protocols, especially in psychology. Recently, it has been shown that measures of R-R variability, especially long-term measures, such as SDNN or ULF power in the 24-hour R-R power spectrum, predict death after myocardial infarction. As univariate predictors, measures of R-R variability predict all-cause mortality as well as left ventricular ejection fraction or unsustained ventricular arrhythmias. When measures of R-R variability are added to other risk predictors (e.g., left ventricular ejection fraction, unsustained ventricular arrhythmias or signal averaged ECG), positive predictive accuracy is improved significantly. Measured either early or late after myocardial infarction, R-R variability predicts death during long-term follow-up. R-R variability predicts arrhythmic events after myocardial infarction even better than all-cause mortality. Since R-R variability is a dynamic variable, it can be used to monitor physiological or pharmacological interventions or the progression of diseases. R-R variability is already established as a useful tool in cardiovascular medicine, but we have much to learn before this tool reaches its full potential. One of the most important questions to answer about R-R variability is whether it is just a risk indicator in coronary heart disease or rather tightly linked mechanistically to arrhythmic deaths in coronary heart disease.

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Chapter 102

Monophasic Action Potential Recording

Michael R. Franz

Recording of monophasic action potentials (MAPs) by contact electrode catheter[1] can be employed easily and safely in the human heart. In contrast to electrocardiographic (ECG) recordings and standard myocardial surface electrograms, which produce a *summative* or *derivative* view of the heart's electrical activity, MAP recordings provide *local* information about the depolarization and repolarization process of myocardial tissue. In fact, MAPs have been validated to reflect single-cell transmembrane action potentials with high accuracy.[2–4] Clinical and experimental MAP recording has been shown useful in the evaluation of antiarrhythmic drug effects on the in situ myocardium, as well as in other areas of human electrophysiology in which an understanding of the relation between ventricular repolarization and refractoriness is important.[5–13] More recently, there has been an emphasis on managing cardiac arrhythmias by non-pharmacological, device-oriented approaches, including automatic defibrillator implantation and radiofrequency catheter ablation. MAP recording aids in the differentiation of ventricular tachycardia and ventricular fibrillation during testing of the implantable defibrillator,[14,15] and provides direct monitoring of myocardial lesion production by radiofrequency energy.[16] Thus, by giving the clinical investigator a more direct view of human myocardial electrophysiology in situ, in both normal and disease states, MAP recordings provide an important bridge between "cellular" and "bedside" electrophysiology. This chapter discusses the methodology and selected clinically pertinent applications of MAP recordings.

MAP RECORDING DEVICES

The first MAPs were recorded in amphibian hearts, long before the discovery of the transmembrane action potential, by techniques that involved traumatization of myocardial tissue.[17,18] These early techniques and the genesis of MAP recordings were discussed in a previous review.[19] The first MAPs from human endocardium were recorded with suction electrode catheters.[20–23] Broad clinical accep-